

# Anhang zur wissenschaftlichen Begründung für die Entscheidung über den Herpes zoster-subunit-Totimpfstoff der Ständigen Impfkommission

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# 1. Suchstrategie und Flussdiagramm des systematischen Reviews zur Wirksamkeit des Herpes zoster-subunit-Totimpfstoffes

## Suchstrategie:

Suche in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, SciSearch, GLOBAL Health und BIOSIS Previews (Datum der Suche: 02.02.2016; Aktualisierung der Suche über Recherche in Embase und Pub-Med: zuletzt am 04.11.2017)

- #1 Herpes zoster OR HZ
- #2 shingl?
- #3 #1 OR #2
- #4 vaccin?
- #5 immunisation OR immunization
- #6 #4 OR #5
- #7 #3 AND #6
- #8 clinical trial OR controlled trial
- #9 random?
- #10 effic?
- #11 #8 OR #9 OR #10
- #12 #7 AND #11

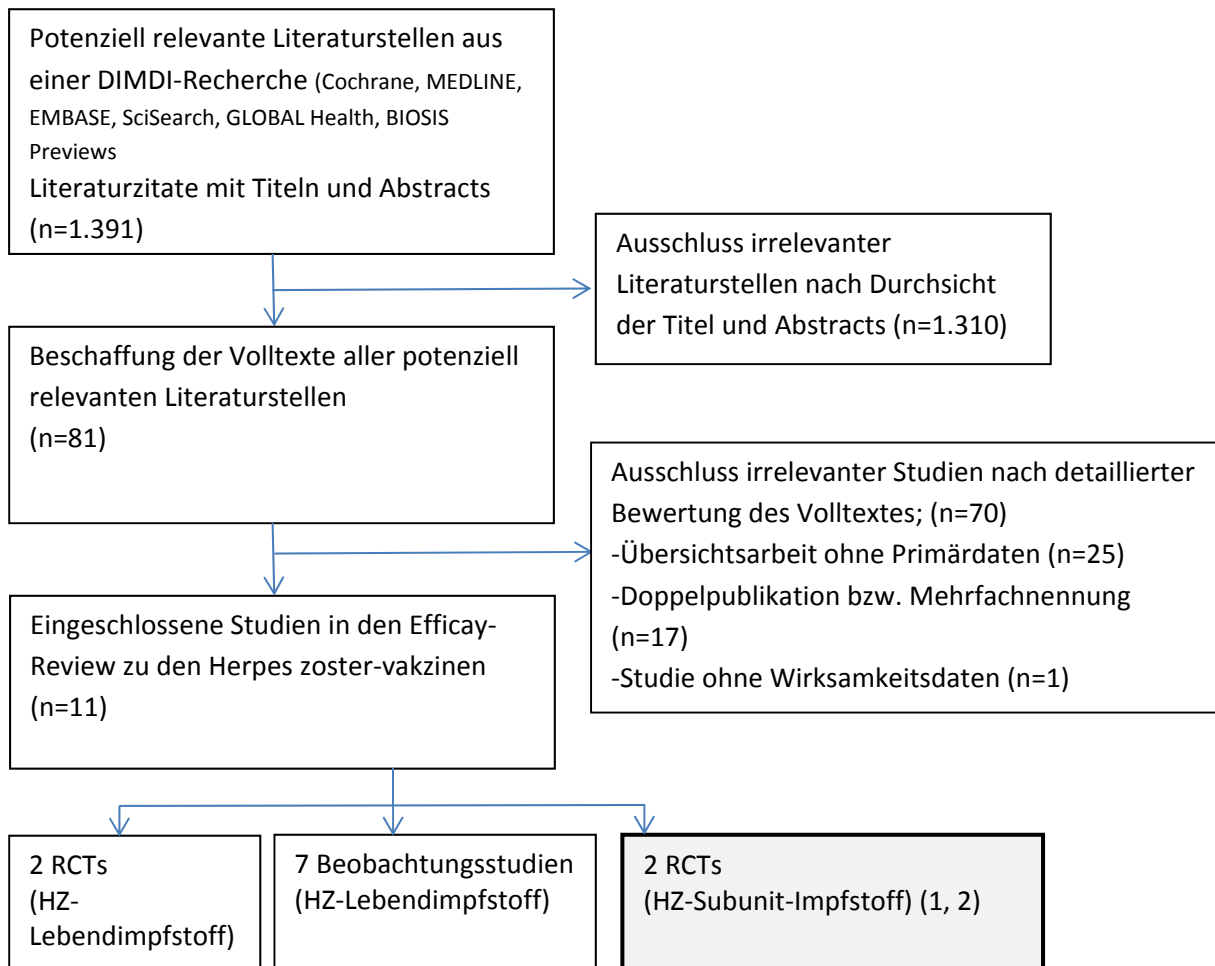


Abbildung 1: Flussdiagramm zum Review der Wirksamkeit und Effektivität (Efficacy und Effectiveness) des Herpes zoster-subunit-Totimpfstoffes

## 2. Suchstrategie und Flussdiagramm des systematischen Reviews zur Sicherheit des Herpes zoster-subunit-Totimpfstoffes

### Suchstrategie:

Suche in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, SciSearch, GLOBAL Health und BIOSIS Previews (Datum der Suche: 08.07.2016; Aktualisierung der Suche über Recherche in Embase und Pub-Med: 04.11.2017)

#1 (Herpes zoster OR HZ) OR shingl?

#2 (vaccin? OR immunization) OR immunization

#3 #1 AND #2

#4 (clinical trial OR controlled trial) OR random? OR safe?

#5 #3 AND #4

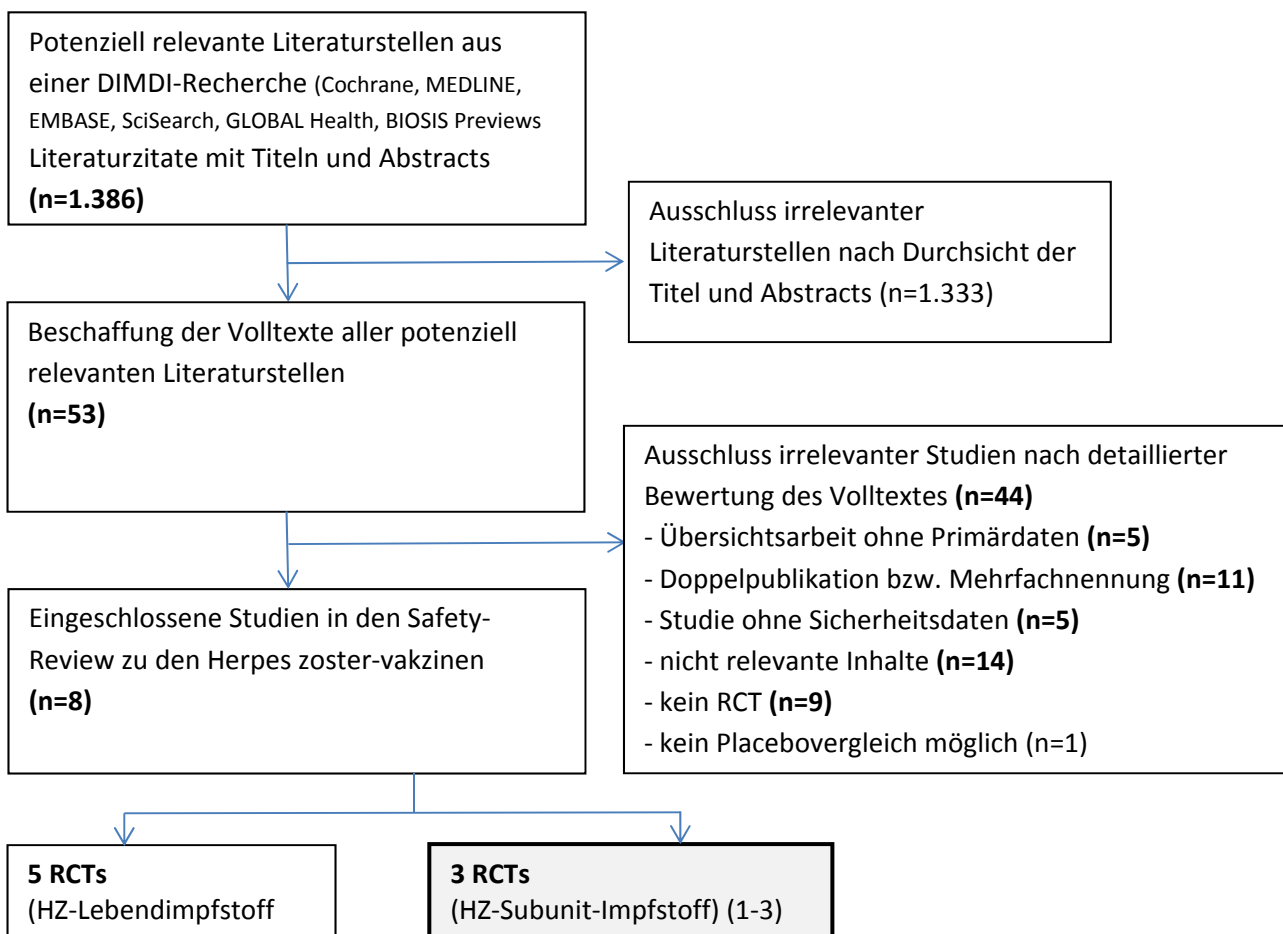


Abbildung 2: Flussdiagramm zum Review der Sicherheit der Herpes zoster-subunit-Totimpfstoffes

### 3. Ein- und Ausschlusskriterien für die Identifikation von relevanten Studien für den systematischen Review zur Wirksamkeit und Sicherheit des Herpes zoster-subunit-Totimpfstoffes

PICO-Kriterium	Einschluss-Kriterium	Ausschluss-Kriterium
<b>P</b>	Personen im Alter $\geq$ 50 Jahren	Andere Altersgruppe
<b>P</b>	Gesunde Erwachsene	Patienten mit bekanntem Grundleiden (z.B. Diabetes mellitus, Immunsuppression etc.)
<b>I</b>	Impfung mit Herpes zoster-s/u-Totimpfstoff	Anderer Impfstoff
<b>C</b>	Impfung mit Placebo	Kein Placebo
<b>O</b>	Outcomes, wie von der Arbeitsgruppe definiert	Andere outcomes, z.B. Immunogenitätsdaten
<b>S</b>	Randomisierte kontrollierte Studien (RCT)	Andere Studiendesigns, Beobachtungsstudien, Fall-Kontroll-Studien, Kohortenstudien <sup>1</sup>
<b>Veröffentlichungszeitraum</b>	Keine zeitlichen Einschränkungen	

P=Population, I=Intervention, C=Comparator, O=Outcome, S=Studien-Charakteristika

## 4. Extraktionen der eingeschlossenen RCTS zur Wirksamkeit des Herpes zoster-subunit-Totimpfstoffes

### 4.1. Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50); Lal (2015)(2)

<b>Study</b>	Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50)
<b>Reference</b>	Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster-subunit-vaccine. <i>N Engl J Med</i> 2015 (372): 2087-96
<b>Country</b>	18 countries in Europe, North America, Latin America, and Asia-Australia
<b>Study period</b>	3,2 years
<b>Study design</b>	ongoing, randomized, placebo-controlled study; 1:1 ratio participants stratified according to region and age group (50 to 59, 60 to 69, and ≥ 70 years)
<b>Objective</b>	To evaluate overall vaccine efficacy in reducing the risk of herpes zoster, as compared with placebo, in adults who were 50 years of age or older. Secondary objectives included determining the vaccine Efficacy in reducing the incidence of herpes zoster in each age group (50 to 59 years, 60 to 69 years, and ≥ 70 years) and HZ/su safety and reactogenicity profiles.
<b>Safety-Substudy</b>	A reactogenicity subgroup of participants recorded solicited injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) on diary cards for 7 days after each vaccination. This subgroup included all participants who were 70 years of age or older and randomly selected participants in the two other age groups (50 to 59 years and 60 to 69 years). The participants rated the intensity of the solicited reactions on a scale from 0 (absent) to 3 preventing normal everyday activities). Unsolicited adverse events were recorded for 30 days after each dose. Serious adverse events were recorded in all participants for up to 12 months after the second dose.
<b>Clinical trial number</b>	Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50),NCT01165177
<b>Randomization</b>	online centralized randomization system
<b>Blinding</b>	Because the appearance of the reconstituted HZ/su vaccine differed from the placebo solution, injections were prepared and administered by study staff who did not participate in any study assessment. The investigators, participants, and those who were responsible for the evaluation of any study end point were unaware of whether vaccine or placebo had been administered: ZOE-50 is ongoing and strict blinding will be maintained until all endpoints are analyzed. All statistical analyses presented in this manuscript were performed by external statisticians according to a pre-defined statistical analysis plan.
<b>Vaccine name (manufacturer)</b>	HZ/su (Shingrix™)
<b>Vaccine composition</b>	The HZ/su vaccine contains 50 µg of recombinant VZV glycoprotein E and the liposome-based AS01 <sub>B</sub> adjuvant system containing 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and 50 µg of Quillaja saponaria Molina, fraction 21 (QS21, Antigenics, a wholly owned subsidiary of Aenus). Investigational recombinant subunit vaccine containing VZV glycoprotein E and the AS01B adjuvant system (called HZ/su, GlaxoSmithKline Biologicals) (Shingrix™)/ VZV glycoprotein E was selected as a candidate vaccine antigen because it is essential for viral replication and cell-to-cell spread and is a primary target of VZV-specific immune responses. The antigen was combined with AS01B because this adjuvant system promotes strong CD4+ T-cell and humoral immune responses against recombinant proteins
<b>Vaccination schedule</b>	two intramuscular doses of the vaccine or placebo 2 months apart into the deltoid muscle
<b>Comparator</b>	Unvaccinated participants
<b>Funding</b>	GlaxoSmithKline Biologicals;

<b>Inclusion criteria</b>	50 years of age or older; Provided written informed consent; comply with the requirements of the protocol (e.g., completion of the diary cards/questionnaires, return for follow-up visits, have regular contact to allow evaluation during the study). female subjects could be enrolled in the study if: they were of non-childbearing potential, defined as current tubal ligation, hysterectomy, ovariectomy or post-menopause; OR they were of childbearing potential if they practiced adequate contraception for 30 days before vaccination, had a negative urine pregnancy test on the day of vaccination, and agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.
<b>Exclusion criteria</b>	history of herpes zoster, previously vaccinated against varicella or herpes zoster, or an immunosuppressive condition/A history of HZ; a history of allergic disease or reactions likely to be exacerbated by any component of the vaccine; Significant underlying illness ; concurrent participation in another clinical study; used any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned to use such a product during the study period; Received immunoglobulins or any blood products within the 90 days preceding the first dose of study vaccine or planned to receive such products during the study period; Administration or planned administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination. However, licensed non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines for seasonal or pandemic flu, with or without adjuvant) could be administered up to 8 days before each dose or at least 14 days after any dose of study vaccine; Any other condition (e.g., extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that, in the opinion of the investigator, might interfere with the evaluations required by the study; Acute disease or fever at the time of enrolment; Chronic administration (defined as > 15 consecutive days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose. For corticosteroids, prednisone < 20 mg/day, or equivalent, was allowed. Inhaled and topical steroids were allowed. Pregnant or lactating; or Planning to become pregnant or planning to discontinue contraceptive precautions (if of childbearing potential).
<b>Efficacy Endpoints</b>	HZ
<b>Identification of HZ</b>	A suspected case of herpes zoster was defined as new unilateral rash with pain (broadly defined to include allodynia, pruritus, or other sensations) that had no alternative diagnosis.
<b>Confirmation of HZ</b>	Each suspected case, the rash was photographed and samples were collected from three lesions to confirm the diagnosis of herpes zoster by means of real-time polymerase-chain reaction (PCR) assay targeting VZV ORF62. The lower limit of detection was 10 VZV DNA copies per reaction. A hierarchical case-definition algorithm was used to classify each suspected case. If the PCR assay was positive for VZV, the case was confirmed. If the PCR assay was negative for VZV and positive for $\beta$ -actin (internal control), the case was classified as not herpes zoster. If all three samples were negative for both VZV and $\beta$ -actin, or if lesion samples were not available, the final diagnosis was determined by unanimous agreement among the five members of an ascertainment committee.
<b>Definition: VE HZ/ VE PHN</b>	$1 - (RR \text{ vacc}) / (RR \text{ unvacc})$
<b>Safety endpoints</b>	Solicited injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia).

<b>Safety-Follow up</b>	A reactogenicity subgroup of participants recorded solicited injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) after each vaccination on diary cards for 7 days. This subgroup included all participants who were 70 years of age or older and randomly selected participants in the two other age groups (50 to 59 years and 60 to 69 years). The participants rated the intensity of the solicited reactions on a scale from 0 (absent) to 3 (preventing normal everyday activities). Unsolicited adverse events were recorded for 30 days after each dose. Serious adverse events were recorded in all participants for up to 12 months after the second dose.
<b>Telephone contact in follow-up period?</b>	Participants were instructed on how to recognize signs and symptoms of herpes zoster and to contact their study site immediately if any developed. They were required to record their symptoms on a specific diary card. Investigators were to examine suspected cases of herpes zoster within 48 hours, if possible. Participants were followed for at least 90 days after the onset of the episode or until the rash resolved and the participant was pain-free for 4 weeks.
<b>Efficacy: Duration of follow-up after vaccination</b>	Starting 1 month after the administration of the second dose, participants were followed for at least 30 months through monthly contacts and through annual visits, which will continue for the entire study period (which is expected to be approximately 60 months)
<b>Initial no. of participants (randomized)</b>	16,160 participants were enrolled between August 2, 2010, and July 21, 2011. Of these participants, 749 were excluded from the efficacy analyses, mostly owing to deviations from Good Clinical Practice standards at two study centers (involving 726 patients).
<b>Final no. of participants (analyzed)</b>	15,411 participants who could be evaluated received either the vaccine (7698 participants) or placebo (7713 participants). 14,759 (95.8%) were included in the modified vaccinated cohort. Most participants received two doses of the study vaccines (95.6% of HZ/su recipients and 96.4% of placebo recipients).
<b>Age at vaccination</b>	Mean age of participants at enrollment was 62.3 years. Identical rates in vaccinated and placebo group.
<b>Sex (%female)</b>	Female (61.2%); Identical rates in vaccinated and placebo group.
<b>Ethnicity</b>	From Europe (51.2%), Asia or Australia (21.3%), Latin America (10.1%; North America (17.4%))// Whites (71.8%), Black (1.8%), Asian (19.1%), Others (7.4%); Identical rates in vaccinated and placebo group.
<b>number with HZ (vaccinated/placebo)</b>	A total of 408 participants reported suspected herpes zoster. Of these participants, 244 (59.8%) were confirmed (220 [90.2%] on PCR assay and 24 [9.8%] by the ascertainment committee). The concordance between the PCR assay results and the committee assessment was 87%. Of the 216 confirmed cases in the modified vaccinated cohort, 6 occurred in the HZ/su group and 210 in the placebo group after a mean follow-up of 3.2 years.
<b>HZ incidence</b>	The overall incidence of herpes zoster per 1000 person-years was 0.3 in the HZ/su group and 9.1 in the placebo group, for an overall vaccine efficacy of 97.2% (95% confidence interval [CI], 93.7 to 99.0; $p < 0.001$ ) among participants who were 50 years of age or older. No significant differences in VE among the age groups (range, 96.6 to 97.9%). The overall vaccine efficacy was similar in the total vaccinated cohort (96.2%; 95% CI, 92.7 to 98.3; $p < 0.001$ ).
<b>Duration and severity of HZ</b>	not reported
<b>number with PHN (vaccinated/placebo)</b>	not reported (will be published in ZOE70)



<b>Adverse events sub study</b>	A total of 8926 participants were assigned to the reactogenicity subgroup (4460 in the HZ/su group and 4466 in the placebo group). Symptoms within 7 days after vaccination were reported in 84.4% of participants in the HZ/su group and 37.8% in the placebo group. Most symptoms were of mild-to-moderate intensity, but 17.0% of HZ/su recipients and 3.2% of placebo recipients reported symptoms that prevented normal everyday activities (grade 3). These symptoms were mostly due to solicited injection-site reactions, which occurred in 81.5% of HZ/su recipients (grade 3 in 9.5%) and 11.9% of placebo recipients (grade 3 in 0.4%), and to systemic reactions, which occurred in 66.1% of HZ/su recipients (grade 3 in 11.4%) and 29.5% of placebo recipients (grade 3 in 2.4%). Pain was the most common injection-site reaction and was reported in 79.1% of HZ/su recipients and 11.2% of placebo recipients. Myalgia was the most common systemic reaction and was reported in 46.3% of HZ/su recipients and 12.1% of placebo recipients. The overall frequencies of solicited reactions were similar after each dose, but grade 3 solicited systemic reactions were more frequent after the second dose (8.5%; 95% CI: 7.7 to 9.4) than after the first dose (5.9%; 95% CI: 5.2 to 6.6).
<b>SAE</b>	Within the first 30 days after vaccination, 231 serious adverse events (103 in HZ/su recipients and 128 in placebo recipients) were reported in 87 of 7698 HZ/su recipients (1.1%) and 97 of 7713 placebo recipients (1.3%) in the total vaccinated cohort. Among these events, 4 participants (1 HZ/su recipient and 3 placebo recipients) had a serious adverse event that was considered to be related to vaccination by the investigators: hypotension with syncope, mononeuritis, neurosensory deafness, and musculoskeletal chest pain.
<b>Cochrane risk of bias tool</b>	
<b>Adequate sequence generation</b>	adequate
<b>Allocation concealment</b>	unclear (not described)
<b>Blinding</b>	adequate
<b>Selective reporting</b>	adequate
<b>Incomplete outcome data</b>	adequate
<b>Other bias</b>	low
<b>Summary: Risk of bias</b>	low
<b>Comments</b>	Efficacy was analyzed in the total vaccinated cohort and in the modified vaccinated cohort (primary analysis); in the latter cohort, participants who did not receive the second dose of vaccine or who received the diagnosis of herpes zoster within 1 month after the second dose were excluded.

#### 4.2. Zoster Efficacy Study in Adults 70 Years of Age or older (ZOE-70); Cunningham (2016)(1)

Study	Zoster Efficacy Study in Adults 70 Years of Age or older
Reference	Cunningham AL, Lal H, et al. Efficacy of the Herpes zoster-subunit-vaccine in Adults 70 Years of Age or Older. <i>New Engl J Med</i> 2016 (375):1019-32
Country	18 countries in Europe, North America, Latin America, and Asia–Australia
Study period	Participants were enrolled in ZOE-70 between August 2, 2010, and July 21, 2011. The last study visit was on July 24, 2015.
Study design	randomized, placebo-controlled, phase 3 trial; same design as ZOE50
Objective	To evaluate the efficacy, immunogenicity, and safety of HZ/su in adults 70 years of age or older.
Clinical trial number	Zoster Efficacy Study in Adults 70 Years of Age or older (ZOE-70),NCT01165229)/50 Years of Age or older (ZOE-50),NCT01165177
Randomization	Participants who were 70 years of age or older were first randomly assigned to either ZOE-50 or ZOE-70 and then were randomly assigned in a 1:1 ratio to either the HZ/su group or the placebo group with the use of an online centralized randomization system.
Blinding	The investigators, participants, and those who were responsible for the evaluation of any study end point were unaware of whether vaccine or placebo had been administered: (ZOE-50 is ongoing and strict blinding will be maintained until all endpoints are analyzed.)
Stratification	Participants were stratified according to region (Asia and Australia, Europe, Latin America, and North America) and age group (70 to 79 years vs. ≥ 80 years [in a 3:1ratio]).
Vaccine name (manufacturer)	HZ/su (Shingrix™)
Vaccine composition	HZ/su contains 50 µg of recombinant VZV glycoprotein E and the liposome-based AS01 <sub>B</sub> adjuvant system (which contains 50 µg of 3-O-desacyl-4'-monophosphoryl lipid A [MPL] and 50 µg of Quillaja saponaria Molina, fraction 21 [QS21, licensed by GSK from Antigenics, a subsidiary of Agenus]).
Vaccination schedule	Vaccine or placebo (0.9% saline solution) was administered (0.5 ml) into the deltoid muscle at month 0 and month 2.
Comparator	Unvaccinated participants
Funding	GlaxoSmithKline Biologicals;
Inclusion criteria	70 years of age or older; provided written informed consent; comply with the requirements of the protocol (e.g., completion of the diary cards/questionnaires, return for follow-up visits, have regular contact to allow evaluation during the study).
Exclusion criteria	history of herpes zoster, previously vaccinated against varicella or herpes zoster, or an immunosuppressive condition/A history of HZ; a history of allergic disease or reactions likely to be exacerbated by any component of the vaccine/ Significant underlying illness that; concurrent participation in another clinical study; /used any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned to use such a product during the study period;/ Received immunoglobulins or any blood products within the 90 days preceding the first dose of study vaccine or planned to receive such products during the study period; /Administration or planned administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination. However, licensed non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines for seasonal or pandemic flu, with or without adjuvant) could be administered up to 8 days before each dose or at least 14 days after any dose of study vaccine; /Any other condition (e.g., extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that, in the

	opinion of the investigator, might interfere with the evaluations required by the study; /Acute disease or fever at the time of enrolment; /Chronic administration (defined as > 15 consecutive days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccine dose. For corticosteroids, prednisone < 20 mg/day, or equivalent, was allowed. Inhaled and topical steroids were allowed.
<b>Efficacy Endpoints</b>	ZOE70: efficacy of HZ/su, as compared with placebo, in reducing the risk of herpes zoster among adults 70 years of age or older/ ZOE50 +ZOE70: to evaluate the efficacy of the vaccine, as compared with placebo, in reducing the risk of herpes zoster and the risk of postherpetic neuralgia in the overall population of participants 70 years of age or older from the two studies. The secondary objectives included the evaluation of vaccine efficacy against postherpetic neuralgia among participants 50 years of age or older and the evaluation of vaccine safety and reactogenicity.
<b>Identification of HZ</b>	A suspected case of herpes zoster was defined as new unilateral rash with pain (broadly defined to include allodynia, pruritus, or other sensations) that had no alternative diagnosis.//
<b>Confirmation of HZ</b>	For each suspected case, the rash was photographed and samples were collected from three lesions to confirm the diagnosis of herpes zoster by means of real-time polymerase-chain reaction (PCR) assay targeting VZV ORF62. The lower limit of detection was 10 VZV DNA copies per reaction. A hierarchical case-definition algorithm was used to classify each suspected case. If the PCR assay was positive for VZV, the case was confirmed. If the PCR assay was negative for VZV and positive for $\beta$ -actin (internal control), the case was classified as not herpes zoster. If all three samples were negative for both VZV and $\beta$ -actin, or if lesion samples were not available, the final diagnosis was determined by unanimous agreement among the five members of an ascertainment committee.
<b>Assessment of PHN</b>	Participants with a suspected case of herpes zoster were asked to attend a schedule of assessment Inventory questionnaire daily for 28 days and weekly thereafter, until the participant had been pain-free for 4 weeks or for at least 90 days after the onset of the rash. The “worst pain” score (item 3: “Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours,” rated on a scale of 0 to 10, with higher numbers indicating worse had postherpetic neuralgia. As in previous studies, postherpetic neuralgia was defined as a worst pain score of 3 or higher for pain that persisted or developed more than 90 days after the onset of herpes zoster rash.
<b>Definition: VE HZ/ VE PHN</b>	$1 - (RR\text{ vacc})/(RR\text{ unvacc})$
<b>Safety endpoints</b>	Solicited injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia).
<b>Safety-Follow up</b>	In ZOE-70, a randomly selected subgroup of age stratified participants recorded injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) on diary cards for 7 days after each injection. Redness and swelling at the injection site were scored as 0 if the affected area was less than 20 mm in diameter, 1 if the affected area was 20 to 50 mm, 2 if the affected area was more than 50 to 100 mm, and 3 if the affected area was more than 100 mm. Fever was scored as 0 for a body temperature The participants rated the intensity of the solicited reactions on a scale from 0 (absent) to 3 preventing normal everyday activities). Unsolicited adverse events were recorded for 30 days after each dose. Serious adverse events were recorded in all participants for up to 12 months after the second dose.

<b>Telephone contact in follow-up period?</b>	Participants were instructed on how to recognize signs and symptoms of herpes zoster and to contact their study site immediately if any developed. They were required to record their symptoms on a specific diary card. Investigators were to examine suspected cases of herpes zoster within 48 hours, if possible. Participants were followed for at least 90 days after the onset of the episode or until the rash resolved and the participant was pain-free for 4 weeks.
<b>Efficacy: Duration of follow-up after vaccination</b>	Starting 1 month after the administration of the second dose, participants were followed for at least 30 months through monthly contacts and through annual visits. Safety was analyzed in the total vaccinated cohort, which included all participants who could be evaluated and who had received at least one dose of HZ/su or placebo. Efficacy was analyzed in the total vaccinated cohort and in the modified vaccinated cohort (the primary cohort for the efficacy analysis), which excluded participants who did not receive the second dose or who had a confirmed herpes zoster episode within 1 month (30 days) after the second dose.
<b>Initial no. of participants (randomized)</b>	A total of 14,816 participants were enrolled and underwent randomization, of whom 916 were excluded from all analyses; 865 of these participants were excluded because of deviations from Good Clinical Practice standards at a study center
<b>Final no. of participants (analyzed)</b>	The remaining 13,900 participants constituted the total vaccinated cohort, 13,163 of whom (94.7%) were included in the modified vaccinated cohort (Fig. 1). Most participants (94.4% of HZ/su recipients and 95.6% of placebo recipients) received both doses. In the pooled analysis of participants from ZOE-70 and ZOE-50, 17,531 participants 70 years of age or older were included in the total vaccinated cohort, and 16,596 were included in the modified vaccinated cohort.
<b>Age at vaccination</b>	Demographic characteristics of the participants at baseline were similar in the two groups. The mean age of the participants at study entry was 75.6 years (range, 62 to 96 years).
<b>Sex (%female)</b>	54,9% were female
<b>Ethnicity</b>	A total of 54.0% of the participants were from Europe, 76.9% were white
<b>number with HZ (vaccinated/placebo)</b>	In the ZOE-70 cohort of the 270 confirmed cases, 246 occurred in the modified vaccinated cohort: 23 in HZ/su recipients and 223 in placebo recipients, after a mean follow-up period of 3.7 years. // In the pooled analysis of participants 70 years of age or older from ZOE-70 and ZOE-50, a total of 25 confirmed cases of herpes zoster occurred in HZ/su recipients, as compared with 284 cases in placebo recipients, which resulted in a vaccine efficacy of 91.3% against herpes zoster (95% CI, 86.8 to 94.5%).
<b>HZ incidence</b>	In the ZOE-70 cohort the incidence of herpes zoster per 1000 person-years was 0.9 in the HZ/su group and 9.2 in the placebo group, for an overall vaccine efficacy of 89.8% (95%confidence interval [CI], 84.2 to 93.7; p<0.001). Vaccine efficacy did not differ significantly between the two age groups (90.0% among participants 70 to 79 years of age and 89.1% among participants ≥ 80 years of age). In The ZOE 50 and ZOE70 Cohort Vaccine efficacy did not differ significantly between the two age groups (91.3% in participants 70 to 79 years of age and 91.4% in participants ≥ 80 years of age); the results were similar in the total vaccinated cohort. The cumulative incidence of herpes zoster was lower in the HZ/su group than in the placebo group Vaccine efficacy was 97.6% during year 1, 92.0% during year 2, 84.7% during year 3, and 87.9% during year 4 after the second vaccination.
<b>Duration and severity of HZ</b>	not reported

<b>number with PHN (vaccinated/placebo)</b>	In the pooled modified vaccinated cohort that included all participants 50 years of age or older, postherpetic neuralgia developed in 4 of 32 HZ/su recipients and in 46 of 477 placebo recipients with herpes zoster, during a mean follow-up period of 3.8 years. The incidence of postherpetic neuralgia per 1000 person-years was 0.1 in the HZ/su group and 0.9 in the placebo group, for a vaccine efficacy of 91.2% among adults 50 years of age or older (95% CI, 75.9 to 97.7%; $p < 0.001$ ). Postherpetic neuralgia did not develop in any HZ/su recipients younger than 70 years of age. Among participants 70 years of age or older, vaccine efficacy against postherpetic neuralgia was 88.8% (95% CI, 68.7 to 97.1%; $p < 0.001$ ). The cumulative incidence of postherpetic neuralgia was lower in the HZ/su group than in the placebo group, in both the modified and the total vaccinated cohorts. The incidence of postherpetic neuralgia among HZ/su recipients with breakthrough herpes zoster did not differ significantly from that among placebo recipients (12.5% and 9.6%, respectively; $p = 0.54$ ).
<b>Adverse events substudy</b>	A total of 8926 participants were assigned to the reactogenicity subgroup (4460 in the HZ/su group and 4466 in the placebo group). Symptoms within 7 days after vaccination were reported in 84.4% of participants in the HZ/su group and 37.8% in the placebo group. Most symptoms were of mild-to-moderate intensity, but 17.0% of HZ/su recipients and 3.2% of placebo recipients reported symptoms that prevented normal everyday activities (grade 3). These symptoms were mostly due to solicited injection-site reactions, which occurred in 81.5% of HZ/su recipients (grade 3 in 9.5%) and 11.9% of placebo recipients (grade 3 in 0.4%), and to systemic reactions, which occurred in 66.1% of HZ/su recipients (grade 3 in 11.4%) and 29.5% of placebo recipients (grade 3 in 2.4%). Pain was the most common injection-site reaction and was reported in 79.1% of HZ/su recipients and 11.2% of placebo recipients. Myalgia was the most common systemic reaction and was reported in 46.3% of HZ/su recipients and 12.1% of placebo recipients. The overall frequencies of solicited reactions were similar after each dose, but grade 3 solicited systemic reactions were more frequent after the second dose (8.5%; 95% CI, 7.7 to 9.4) than after the first dose (5.9%; 95% CI, 5.2 to 6.6). Within the first 30 days after vaccination, 231 serious adverse events (103 in HZ/su recipients and 128 in placebo recipients) were reported in 87 of 7698 HZ/su recipients (1.1%) and 97 of 7713 placebo recipients (1.3%) in the total vaccinated cohort. Among these events, 4 participants (1 HZ/su recipient and 3 placebo recipients) had a serious adverse event that was considered to be related to vaccination by the investigators: hypotension with syncope, mononeuritis, neurosensory deafness, and musculoskeletal chest pain.
<b>Cochrane risk of bias tool</b>	
<b>Adequate sequence generation</b>	adequate
<b>Allocation concealment</b>	unclear (not described)
<b>Blinding</b>	adequate
<b>Selective reporting</b>	adequate
<b>Incomplete outcome data</b>	adequate
<b>Other bias</b>	low
<b>Summary: Risk of bias</b>	low
<b>Comments</b>	Efficacy was analyzed in the total vaccinated cohort and in the modified vaccinated cohort (primary analysis); in the latter cohort, participants who did not receive the second dose of vaccine or who received the diagnosis of herpes zoster within 1 month after the second dose were excluded.

## 5. Extraktionen der eingeschlossenen RCTs zur Sicherheit des adjuvantierten Herpes zoster-subunit-Totimpfstoffes

### 5.1. Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50); Lal (2015)(2)

Extraktion der Zoster Efficacy Study in Adults 50 ≥ years (ZOE-50) sind unter 4.1. aufgeführt.

### 5.2. Zoster Efficacy Study in Adults 70 Years of Age or older (ZOE-70); Cunningham (2016)(1)

Extraktion der Zoster Efficacy Study in Adults 70 ≥ years (ZOE-70) sind unter 4.2. aufgeführt.

### 5.3. Safety and immunogenicity of an AS01-adjuvanted varicella-zoster virus subunit candidate vaccine against herpes zoster in adults ≥ 50 years of age; Chlibek (2013)(3)

<b>Study</b>	<b>Safety: II.29_Chlibek</b>
<b>Reference</b>	Chlibek R et al.; Safety and immunogenicity of an AS01-adjuvanted varicella-zoster-virus subunit candidate vaccine against herpes zoster in adults ≥ 50 years of age. J Infect Dis. 2013 Dec 15;208(12)
<b>Country</b>	Czech Republic (n=1), Spain (n=4), United States (n=7)
<b>Study period</b>	January 12 - July 2, 2010
<b>Study design</b>	phase II, observer-blind, parallel group, placebo controlled, randomized, multinational study
<b>Clinical trial number</b>	<a href="#">NCT00802464</a>
<b>Randomization</b>	Subject enrollment was stratified by age at a ratio of 4:4:3:1 for 50–59 years, 60–69, 70–79, and ≥ 80 years of age. Subjects were randomized 4:4:2:1 to be vaccinated with 2 doses, 2 months apart (months 0, 2) of gE/AS01 <sub>B</sub> , gE/AS01 <sub>E</sub> , gE/ saline, or saline alone (placebo). Treatments were allocated at each site using a central randomization system on the Internet. The randomization was made using an algorithm that stratified by country, minimized for age, and included a block size of 11. After having checked that a subject was eligible, and after informed consent had been obtained, the person in charge of the vaccination accessed the randomization system on internet using the subject number and age.
<b>Blinding</b>	Both vaccine recipients and observers responsible for evaluations were blinded to which formulation was administered.
<b>Vaccine name (manufacturer)</b>	GSK
<b>Vaccine composition</b>	Recombinant VZV gE contained 50 µg purified gE mixed with 0.5 mL Saline or AS01 <sub>B</sub> or AS01 <sub>E</sub>
<b>Vaccination schedule</b>	2 doses 2 months apart; All vaccines were administered by intramuscular injection in the upper deltoid site of the non-dominant arm.
<b>Comparator</b>	Saline = placebo
<b>Funding</b>	GlaxoSmithKline Biologicals SA, Belgium.
<b>Inclusion criteria</b>	The study included adults ≥ 50 years of age.
<b>Exclusion criteria</b>	Subjects using any investigational or nonregistered drug or vaccine within 30 days preceding 1st dose or any non-replicating vaccines within 2 weeks of enrollment, were receiving chronic (> 14 days) immunosuppressants or other immune-modifying drugs within 3 months prior to enrollment, were previously vaccinated against HZ or varicella, had a history of HZ, allergic disease or reactions likely to be exacerbated by any component of the vaccine, had a confirmed or suspected immunosuppressive or immunodeficient condition, were administered immunoglobulins or any blood products within the 3 months preceding the first injection of study vaccine or planned to receive them during the study period, or had an acute disease at enrollment. In addition, women could not be pregnant or had to be using birth control or be of non-

	childbearing potential.
<b>Safety endpoints</b>	Local (pain, redness, and swelling) or general (fatigue, fever, headache, gastrointestinal symptoms, and myalgia) solicited symptoms, unsolicited symptoms. Redness and swelling at the injection site were scored as 0 for < 20 mm diameter, 1 for ≥ 20 to ≤ 50 mm, 2 for > 50 to ≤ 100 mm, or 3 for > 100 mm. Temperature was scored as 0 for < 37.5°C, 1 for 37.5°C to 38.0°C, 2 for 38.1°C to 39.0°C, or 3 for > 39.0°C. All other symptoms were scored as 0 for absent, 1 for easily tolerated, 2 for interferes with normal activity, or 3 for prevents normal activity. Investigators recorded causality as “no” for not causally related or “yes” for related or a reasonable possibility of relatedness. Severe adverse events (SAEs) were defined as events that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, caused a congenital anomaly/birth defect in the child of a study subject, or could have jeopardized the subject or required medical or surgical intervention.
<b>Safety-Follow up</b>	Subjects recorded on a diary card the occurrence of local or general solicited symptoms between days 0 and 6, and the occurrence of unsolicited symptoms between days 0 and 29 after each dose. Severe adverse events (SAEs) were collected for 1 year after the last vaccination
<b>Initial no. of participants (randomized)</b>	A total of 410 subjects were enrolled in the study, including 150 who received gE/AS01 <sub>B</sub> , 149 who received gE/AS01 <sub>E</sub> , 73 who received gE/Saline, and 38 who received saline. All subjects were seropositive for anti-VZV and anti gE antibodies at enrollment.
<b>Final no. of participants (analyzed)</b>	Of the 410 subjects, 395 completed the study.
<b>Age at vaccination</b>	The mean age was approximately 65 years in all groups (mean ± standard deviation, 65 ± 9.0 years for saline, 65.1 ± 8.7 for gE/saline, 65.1 ± 9.9 for gE/AS01 <sub>E</sub> , 65.0 ± 8.9 for gE/AS01 <sub>B</sub> ).
<b>Sex (% male)</b>	Just over half of the subjects were women in all groups (57.9% for saline, 54.8% for gE/saline, 59.7% for gE/AS01 <sub>E</sub> , 54.0% for gE/AS01 <sub>B</sub> ).
<b>Ethnicity</b>	Most were of Caucasian/European heritage (100.0% for saline, 98.6% for gE/saline, 97.3% for gE/AS01 <sub>E</sub> , 64.0% for gE/AS01 <sub>B</sub> ).
<b>Safety Results</b>	The most common symptoms in all groups were solicited local symptom was injection site pain. The most common solicited general symptoms were fatigue, myalgia, and headache. The frequency of general and local symptoms was higher with adjuvanted than with unadjuvanted gE, which was higher than for saline alone. Between 8% and 10% of all subjects receiving adjuvanted gE experienced a grade 3 reaction (9.3% for gE/AS01 <sub>B</sub> , 8.1% for gE/AS01 <sub>E</sub> ) vs 5.3% for saline and 2.7% for gE/saline. The most common of these were fatigue, myalgia, and injection site pain, and in most cases, they resolved within 3 days. The only unsolicited symptom reported by > 3% of subjects in any group was chills, which was reported by 5% (8/150) of subjects treated with gE/AS01 <sub>B</sub> and 2% (3/149) of those treated
<b>SAE</b>	Two vaccine-related adverse events led to withdrawal from the study: one subject treated with gE/AS01 <sub>B</sub> withdrew due to malaise beginning on the day of vaccination, and one subject treated with gE/AS01 <sub>E</sub> withdrew due to injection site redness that lasted > 2 weeks. No vaccine-related SAEs and no cases of HZ were reported through month 14 of the study.
<b>Cochrane risk of bias tool</b>	
<b>Adequate sequence generation</b>	low risk
<b>Allocation concealment</b>	low risk
<b>Blinding</b>	low risk

<b>Selective reporting</b>	adequate
<b>Incomplete outcome data</b>	adequate
<b>Other bias</b>	unclear
<b>Summary: Risk of bias</b>	low risk
<b>Comments</b>	

## 6. Lokalreaktionen und systemische Reaktionen in der ZOE-70 Studie nach Ausprägung und Dauer (1)

		HZ/su-Impfstoff		Placebo	
		Häufigkeit n/(%)	mediane Dauer (d)	Häufigkeit (%)	mediane Dauer (d)
<b>Lokalreaktionen</b>		(Dosen: n=994)		(Dosen: n=995)	
<b>Schmerzen</b>	Alle	579/ (58,2)	2	49/ (4,9)	1
	Grad 3	24/ (2,4)	1,5	1/ (0,1)	7
<b>Rötung</b>	Alle	280/ (28,2)	3	6/ (0,6)	2,5
	Grad 3	24/ (2,4)	2	0	-
<b>Schwellung</b>	Alle	153/ (15,4)	3	2/ (0,2)	1,5
	Grad 3	9/ (0,9)	1	0	-
<b>Systemische Reaktionen</b>		(Dosen: n=993)		(Dosen=992)	
<b>Fatigue</b>	Alle	226/ (22,8)	2	95/ (9,6)	2
	Grad 3	17/ (1,7)	1	4/ (0,4)	2,5
<b>Myalgie</b>	Alle	219/ (22,1)	2	45/ (4,5)	2
	Grad 3	13/ (1,3)	2	2/ (0,2)	5
<b>Kopfschmerz</b>	Alle	148/ (14,9)	2	68/ (0,7)	2
	Grad 3	6/ (0,6)	1	4/ (0,4)	2,5
<b>Schüttelfrost</b>	Alle	97/ (9,8)	1	28/ (2,8)	2
	Grad 3	6/ (0,6)	1	2/ (0,2)	1
<b>Fieber</b>	Alle	77/ (7,8)	2	15/ (1,5)	1
	Grad 3	0	-	4/ (0,4)	1



## 7. Mit der Impfung in Verbindung stehende schwerwiegende unerwünschte Ereignisse (Vaccine related serious adverse events (SAE)) in den eingeschlossenen Studien zur Sicherheit des Herpes zoster-subunit-Totimpfstoffes (1-3)

Studie (Jahr), Altersgruppe, Follow-up-Zeitraum	Teilnehmer Gesamt: (Studiengruppe/ Kontrollgruppe)	SAEs möglicherweise oder wahrscheinlich mit Impfung assoziiert	SAE mit HZ-subunit-Totimpfstoff assoziiert	SAE in der Kontrollgruppe
			n/ (%)	n/ (%)
<b>ZOE-50</b> (2015), ≥ 50 Jahre, 3,5 Jahre (2);	Gesamt: n=15.411 (Impfstoffgruppe: n=7.698/ Placebogruppe: n=7.713)	n=4	n=1 (< 0,1%) Hypotension mit Synkope	n=3 (< 0,1%) Mononeuritis, neurosensorische Taubheit, muskuloskelettaler Brustschmerz
<b>ZOE-70</b> (2016), ≥ 70 Jahre, 4 Jahre (1)	Gesamt: n=13.900 (n=Impfstoffgruppe: n=6.950/ Placebogruppe: n=6.950)	n=20	n=12 (0,2%) Lymphadenitis, Myokardinfarkt, ulcerative Colitis, Pankreatitis, Erythem und Schmerzen an der Injektionsstelle, Schüttelfrost, Fieber, allergische granulomatöse Gefäßentzündung, bakterielle Gelenkentzündung, Erysipel, Herpes zoster oticus, Ekzem, neutropenische Sepsis, akute myeloische Leukämie	n=8 (0,1%) Polymyalgia rheumatica, Adenokarzinom des Magens, Zerebralinfarkt, Guillain-Barré-Syndrom, Bewusstseinsverlust, Synkope, Glomerulonephritis
<b>Chlibek</b> (2013), ≥ 50 Jahre, 14 Monate (3)	Gesamt: n=188 (n=Impfstoffgruppe: n=150/ Placebogruppe: n=38)	n=0	-	-

## 8. Literatur zum Anhang

1. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Diez-Domingo J, et al. Efficacy of the Herpes zoster-subunit-vaccine in Adults 70 Years of Age or Older. *N Engl J Med.* 2016;375(11):1019-32.
2. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster-subunit-vaccine in older adults. *N Engl J Med.* 2015;372(22):2087-96.
3. Chlibek R, Bayas JM, Collins H, de la Pinta ML, Ledent E, Mols JF, et al. Safety and immunogenicity of an AS01-adjuvanted varicella-zoster virus subunit candidate vaccine against herpes zoster in adults  $\geq 50$  years of age. *J Infect Dis.* 2013;208(12):1953-61.

## 9. Evidence-to-Decision Tabelle: Soll der Herpes zoster (HZ)-subunit-Totimpfstoff für eine Standardimpfung (S) zur Verhinderung von Herpes zoster generell empfohlen werden?

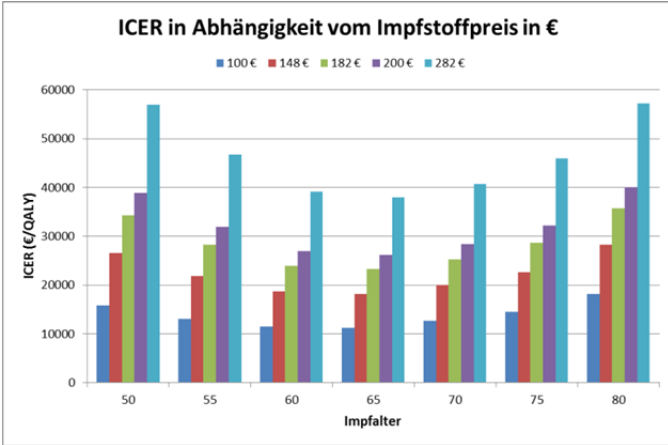
Impfziel: Reduzierung der Krankheitslast von Herpes zoster und den damit verbundenen Komplikationen

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise
Problem	Hat das Problem Priorität?	<input type="checkbox"/> Nein <input type="checkbox"/> Eher Nein <input type="checkbox"/> Unklar <input type="checkbox"/> eher Ja <input checked="" type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	<p><b>HZ-Inzidenz in Deutschland (1, 2):</b></p> <ul style="list-style-type: none"> <li>• Total: 6 HZ-Fälle/ 1.000 Einwohner (Frauen &gt; Männer)</li> <li>• &lt;50 Jahre: 4 HZ-Fälle/1.000 Personenjahre (PJ)<sup>§</sup></li> <li>• Inzidenzanstieg ab 50 Jahre von 6,2 HZ-Fälle/1.000 PJ<sup>§</sup> bei 50-54-Jährigen auf bis zu 14 HZ-Fälle/1000 PJ bei 80-89-Jährigen<sup>§</sup></li> </ul> <p><b>Krankenhaus Diagnosedaten (Durchschnitt der Jahre 1995-2012):<sup>&amp;</sup></b></p> <ul style="list-style-type: none"> <li>• 20–49 Jahre: 6.7 HZ-Fälle/100.000 Einwohner</li> <li>• ≥90 Jahre: 57,7 HZ-Fälle/100.000 Einwohner</li> <li>• Stetiger Inzidenzanstieg über die Zeit von 9/100.000 Einwohner 1995 auf 17/100,000 in 2012</li> </ul> <p><b>HZ-Inzidenz bei Patienten mit Immundepression oder Immundefizienz</b> ist doppelt so hoch wie bei immunkompetenten Personen (12 vs. 6 HZ-Fälle /1.000 PJ)(2)</p> <p><b>HZ-Mortalität:</b></p> <ul style="list-style-type: none"> <li>• ≥50 Jahre: 75 HZ-Sterbefälle/Jahr, 2005-2014<sup>*</sup></li> <li>• ≥50 Jahre: 0.21/ 100.000 Einwohner<sup>§</sup></li> </ul> <p><b>PHN-Inzidenz in Deutschland:</b></p> <ul style="list-style-type: none"> <li>• 0,43 - 1,33/1.000 PJ, (♀&gt;♂)(1)</li> <li>• 11,5% - 14,9% der HZ-Fälle &gt;50 Jahre entwickeln PHN</li> <li>• Inzidenz steigt mit zunehmendem Alter (2)</li> </ul> <p><b>HZ-Komplikationen (außer PHN) bei 28% der HZ-Fälle: (2)</b></p> <ul style="list-style-type: none"> <li>• Mitbeteiligung des Nervensystems (15.5%)</li> <li>• Zoster ophthalmicus (4.8%)</li> <li>• Disseminierter HZ (0.6%)</li> <li>• Zosterenzephalitis (0.4%)</li> <li>• Zoster meningitis (0.1%)</li> </ul> <p><sup>*</sup>Todesursachenstatistik, (<a href="http://www.gbe-bund.de">www.gbe-bund.de</a>)  <sup>§</sup>Abrechnungsdaten der gesetzlichen Krankenversicherung  <sup>§</sup>Versicherungsdaten  <sup>&amp;</sup>Krankenhausdiagnosedaten (Hauptdiagnosen) (<a href="http://www.gbe-bund.de">www.gbe-bund.de</a>)</p>	<p>HZ-Inzidenz steigt mit zunehmendem Alter an, steiler Anstieg ab einem Alter von 50 Jahren bis zum Alter von ca. 70 Jahren, ab 70+ Jahre Inzidenzplateau;          Höchste altersspezifische Inzidenz der PHN ab einem Alter von ca. 80 Jahren</p> <p>Immunsupprimierte (z.B. HIV-Infizierte, Patienten nach Organ- oder Stammzelltransplantation, Patienten mit einer bösartigen Tumorerkrankung) erkranken häufiger an HZ: Inzidenzraten um 80% höher          Bei Immunsupprimierten ist der Anteil an Patienten, die eine PHN entwickeln, um 36% höher          Immunsupprimierte erleiden häufiger Komplikationen der HZ-Erkrankung (31% vs. 27%)(2)</p>

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise
Nutzen und Risiken	Sind die zu erwartenden erwünschten Effekte groß?	<input type="checkbox"/> Nein <input type="checkbox"/> Eher Nein <input type="checkbox"/> Unklar <input type="checkbox"/> Eher Ja <input checked="" type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	<p><b>Impfeffektivität (systematischer Review) (3, 4):</b></p> <ul style="list-style-type: none"> <li>- gegenüber Herpes zoster 50+ Jahre: 92% (89,9 – 94,0)</li> <li>- Altersgruppe 50-59J: 97% (90,0 – 99,0)</li> <li>- Altersgruppe 60-69J: 94% (85,0 – 98,0)</li> <li>- Altersgruppe 70-79J: 90% (85,0 – 93,0)</li> <li>- Altersgruppe 80+J: 90% (79,0 – 95,0)</li> <li>-</li> <li>- gegenüber PHN: 82% (64,0 – 91,0)</li> <li>- Altersgruppe 50-59J: 95% (9,0 – 100,0)</li> <li>- Altersgruppe 60-69J: 86% (-145,2 – 100,0)</li> <li>- Altersgruppe 70-79J: 87% (63,0 – 95,0)</li> <li>- Altersgruppe 80+J: 4% (-124,3 – 84)</li> <li>- Dauer der Wirksamkeit: 4 Jahre nach Impfung &gt;85% (bei Alter 70+J)</li> </ul> <p><b>Statistisches Markov Kohorten-Model (5):</b>            Bei einer Impfquote von of <b>35,5% und Impfung im Alter von 60 Jahren</b> sind in einer Kohorte von 1Mio 50-Jähriger, die bis zum Lebensende verfolgt wird, folgende Effekte zu erwarten:</p> <ul style="list-style-type: none"> <li>- Verhinderung von 21.924 HZ- und von 1.376 PHN-Fällen</li> </ul> <p><b>Bei Impfung im Alter von 65 Jahren:</b></p> <ul style="list-style-type: none"> <li>- Verhinderung von 21.740 HZ- und von 1.501 PHN-Fällen</li> </ul> <p><b>Bei Impfung im Alter von 70 Jahren:</b></p> <ul style="list-style-type: none"> <li>- Verhinderung von 19.255 HZ- und von 1.521 PHN-Fällen</li> </ul> <p><b>Zahl der notwendigen Impfungen um einen Fall zu verhindern (Number needed to vaccinate, NNV), bei Impfung mit 60, 65, 70 Jahren:</b></p> <ul style="list-style-type: none"> <li>- NNV zur Verhinderung eines HZ-Falles: 15, 15, 16</li> <li>- NNV zur Verhinderung eines PHN-Falles: 244, 214, 197</li> </ul>	<p>Leichter Rückgang der Impfeffektivität mit höherem Alter; Wirksamkeit bleibt über 89% in allen Altersgruppen</p> <p>Impfeffektivität relativ stabil über 4 Jahre nach Impfung: ganz leichter Rückgang von 92% im Jahr 2 auf 88% im Jahr 4</p> <p>Immunologische Daten zeigen 9 Jahre nach Impfung noch um ein Vielfaches höhere anti-gE-Antikörperspiegel und CD4+-Zellzahlen als vor der Impfung (6-9)</p> <p>Variation der Modellannahmen:            Impfen mit 60 bei Impfquote von 60%:            - Verhinderung von 37.264 HZ-Fällen            Impfen mit 60 bei Impfquote von 80%:            - Verhinderung von 49.685 HZ-Fällen</p>

Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise												
Sind die zu erwartenden unerwünschten Effekte gering?	<input type="checkbox"/> Nein <input checked="" type="checkbox"/> Eher Nein <input type="checkbox"/> Unklar <input type="checkbox"/> Eher Ja <input type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	<p><b>Lokalreaktionen (3, 4, 10):</b>            Lokalreaktionen insgesamt häufiger in der Impfstoff- im Vergleich zur Placebo-Gruppe; schwere Lokalreaktionen (Grad 3) im 1-stelligen %-Bereich und nahezu ausschließlich in der Impfstoffgruppe            Anteil in Impfstoff- vs. Placebogruppe (Grad3)</p> <ul style="list-style-type: none"> <li>Schmerzen 58,2% vs. 4,9% (2,4% vs. 0,1%)</li> <li>Rötung 28,2% vs. 0,6 (2,4% vs. 0,0)</li> <li>Schwellung 15,4% vs. 0,2 (0,9% vs. 0,0)</li> <li>mittlere Dauer: 2 - 3 Tage</li> </ul> <p><b>Systemische Reaktionen insgesamt häufiger in der Impfstoffgruppe, Grad3-Reaktionen jedoch nahezu gleich häufig:</b>  <b>Anteil in Impfstoff- vs. Placebogruppe (Grad3) (3, 4, 10):</b></p> <ul style="list-style-type: none"> <li>Fieber: 7,8% vs. 1,5% (0 vs. 0,4%)</li> <li>Myalgie: 22,1% vs. 4,5% (1,3% vs. 0,2)</li> <li>Kopfschmerzen: 14,9% vs. 0,7% (0,6% vs. 0,4%)</li> <li>Müdigkeit: 22,8% vs. 9,6% (1,7% vs. 0,4%)</li> <li>Mittlere Dauer: 1 - 2 Tage</li> </ul> <p>- Kein Signal für potenzielle Autoimmunerkrankungen: 1,2% vs. 1,3%</p> <p>- Kein Signal für schwere unerwünschte Nebenwirkungen (0,1% vs. 0,1%)</p> <p>- keine impfbedingten Todesfälle</p>	<p>Keine Sicherheitsbedenken bei Impfung von Patienten mit durchgemachter HZ-Epidsode (11)</p> <p>Keine Sicherheitsbedenken bei Impfung von Personen, die zuvor mit HZ-Lebendimpfstoff geimpft worden waren (12)</p>												
Sind die erwünschten Effekte groß in Relation zu den unerwünschten Effekten?	<input type="checkbox"/> Nein <input type="checkbox"/> Eher Nein <input type="checkbox"/> Unklar <input type="checkbox"/> Eher Ja <input checked="" type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	<ul style="list-style-type: none"> <li>HZ und PHN traten deutlich seltener in der Impfstoffgruppe auf</li> <li>Dauer des Impfschutzes ist bisher über 4 Jahre mit klinischem Endpunkt HZ belegt</li> <li>Immunologische Daten zeigen 9 Jahre nach Impfung noch um ein Vielfaches höhere anti-gE-Antikörperspiegel und CD4+-Zellzahlen als vor der Impfung</li> <li>Schwere unerwünschte Nebenwirkungen waren selten und ihre relative Häufigkeit unterschied sich nicht in Impfstoff- und Placebo-Gruppe</li> </ul>	<p>Impfstoff war gut verträglich und mit befriedigender Immunantwort bei Patienten nach autologer Stammzelltransplantation und bei HIV-Infizierten (2 Beobachter-geblindete Placebo-kontrollierte Phase 1/2a Studien – (13, 14))</p>												
Wie ist die Qualität der Evidenz?	<p><b>Wirksamkeit der Intervention</b></p> <input type="checkbox"/> keine Studien <input type="checkbox"/> sehr niedrig <input type="checkbox"/> niedrig <input checked="" type="checkbox"/> moderat <input type="checkbox"/> hoch	<p>Relative Bedeutung der wichtigsten Ergebnisse bzw. Endpunkte:</p> <table border="1" data-bbox="913 1209 1594 1359"> <thead> <tr> <th data-bbox="913 1209 1167 1267">Ergebnis</th> <th data-bbox="1167 1209 1346 1267">relative Bedeutung</th> <th data-bbox="1346 1209 1594 1267">GRADE</th> </tr> </thead> <tbody> <tr> <td colspan="3" data-bbox="913 1267 1594 1299"><b>Wirksamkeit der Intervention</b></td> </tr> <tr> <td data-bbox="913 1299 1167 1331">Herpes zoster</td> <td data-bbox="1167 1299 1346 1331">CRITICAL</td> <td data-bbox="1346 1299 1594 1331">HIGH</td> </tr> <tr> <td data-bbox="913 1331 1167 1359">PHN</td> <td data-bbox="1167 1331 1346 1359">CRITICAL</td> <td data-bbox="1346 1331 1594 1359">LOW</td> </tr> </tbody> </table> <p><b>Sicherheit der Intervention</b></p>	Ergebnis	relative Bedeutung	GRADE	<b>Wirksamkeit der Intervention</b>			Herpes zoster	CRITICAL	HIGH	PHN	CRITICAL	LOW	
Ergebnis	relative Bedeutung	GRADE													
<b>Wirksamkeit der Intervention</b>															
Herpes zoster	CRITICAL	HIGH													
PHN	CRITICAL	LOW													

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz			zusätzliche Hinweise
		<b>Sicherheit der Intervention</b> <input type="checkbox"/> keine Studien <input type="checkbox"/> sehr niedrig <input type="checkbox"/> niedrig <input checked="" type="checkbox"/> moderat <input type="checkbox"/> hoch	Schmerzen	CRITICAL	MODERATE	
			Impfbedingte systemische Nebenwirkungen	IMPORTANT	HIGH	
			Fieber	CRITICAL	HIGH	
			Impfbedingte schwere unerwünschte Wirkungen	CRITICAL	MODERATE	
			Autoimmunerkrankungen	CRITICAL	MODERATE	
Werte	Besteht erhebliche Unsicherheit darüber, ob die Intervention Akzeptanz in der Zielgruppe findet? (Nutzen-Risiko-Bewertung auf Patientenebene)	<input type="checkbox"/> Erhebliche Unsicherheit oder Variabilität <input checked="" type="checkbox"/> Mögliche Unsicherheit oder Variabilität <input type="checkbox"/> Eher keine Unsicherheit oder Variabilität <input type="checkbox"/> Keine Unsicherheit oder Variabilität <input type="checkbox"/> keine bekannten unerwünschten Endpunkte	Beobachtungsstudien zeigten, dass HZ und PHN mit einer erheblichen Beeinträchtigung der Lebensqualität einhergehen: beeinträchtigt waren die Ausführung von Routinetätigkeiten, die Mobilität, die Arbeit, der Schlaf, Stimmung und soziale Kontakte der Betroffenen. (15, 16) Die Mehrheit der Familienangehörigen (69% der Kinder; 80% der Lebenspartner) von Patienten mit HZ oder PHN berichtete, dass die Pflege der Patienten moderate bis starke Auswirkungen auf das eigene Leben hatte. (17) Die wahrgenommene Krankheitslast ist damit sicher groß. Welchen Einfluss diese Einschätzung der Beeinträchtigung der Lebensqualität durch HZ und PHN auf die tatsächliche Inanspruchnahme der Impfung haben wird, ist jedoch nicht klar belegt.			Hohe Reaktogenität bzw. ungünstiges Erleben der ersten Impfstoffdosis könnte Bereitschaft für die 2. Impfung beeinträchtigen
Ressourcen	Sind die erforderlichen Ressourcen gering?	<input type="checkbox"/> Nein <input type="checkbox"/> Eher Nein <input checked="" type="checkbox"/> Unklar <input type="checkbox"/> Eher Ja <input type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	Preis: 113,40 EUR pro Impfstoffdosis plus Administration			Gesundheitsökonomische Bewertung führt nicht zur Entscheidung ob die Intervention eingeführt wird, sondern ab welchem Alter die Intervention am besten eingeführt werden kann, damit sie die größte Wirkung entfaltet

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise
	Sind die inkrementellen Kosten niedrig im Vergleich zum Gesamtnutzen?	<input type="checkbox"/> Nein <input type="checkbox"/> Eher Nein <input type="checkbox"/> Unklar <input checked="" type="checkbox"/> Eher Ja <input type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	<p><b>Kosten-Effektivitäts-Analyse (5)</b></p>  <p>In der Sensitivitätsanalyse erwiesen sich die</p> <ul style="list-style-type: none"> <li>- Dauer des Impfschutzes,</li> <li>- der Impfstoffpreis und</li> <li>- das angenommene Risiko für weitere HZ-Episoden (Rezidive)</li> </ul> <p>als die Variablen mit dem größten Einfluss auf die Modellergebnisse.</p>	(ICERs noch nicht an realen Impfstoffpreis angepasst – dieser wird zwischen 200 und 282 EUR liegen; damit ändern sich die ICERs nach Impfalter noch im Wert aber nicht in der Tendenz!)
Gleichheit	Hätte die Intervention aus Public Health Perspektive Auswirkung auf Ungleichgewichte bez. Gesundheit? (Würden Bevölkerungsgruppen von der Intervention benachteiligt?)	<input type="checkbox"/> Ungleichheit sicher verstärkt <input type="checkbox"/> Ungleichheit eher verstärkt <input type="checkbox"/> Unklar <input checked="" type="checkbox"/> Ungleichheit eher verringert <input type="checkbox"/> Ungleichheit verringert <input type="checkbox"/> Teils / Teils	Entscheidung der STIKO zur Standardimpfung würde zumindest für Personen im empfohlenen Impfalter die Ungleichheit verringern, weil für diese dann einheitliche Grundsätze gelten und insbes. wenn die Kosten für die Impfung von den GKV übernommen werden	Kostenerstattung auf Basis der STIKO-Empfehlung durch den G-BA zu regeln

	Kriterien	Bewertung	Stand der Wissenschaft / Evidenz	zusätzliche Hinweise
Akzeptanz (Umsetzungsbereitschaft?)	Wird die Option / Empfehlung von Entscheidungsträgern akzeptiert?	<input type="checkbox"/> Nein <input type="checkbox"/> Eher Nein <input type="checkbox"/> Unklar <input checked="" type="checkbox"/> Eher Ja <input type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	<ul style="list-style-type: none"> <li>• Empfehlung einer Impfung durch den behandelnden Arzt spielt Hauptrolle für Impfentscheidung eines Patienten (18, 19)</li> <li>• Impfinanspruchnahme steigt nach Zoster-Erkrankung des Partners (20).</li> <li>• Individuelle Impfentscheidung wird durch Wissen über die Erkrankung und die persönliche Risiko-Abwägung beeinflusst (21)</li> </ul>	
Durchführbarkeit	Ist die Intervention (Impfempfehlung) umsetzbar?	<input type="checkbox"/> Nein <input type="checkbox"/> Eher Nein <input type="checkbox"/> Unklar <input type="checkbox"/> Eher Ja <input checked="" type="checkbox"/> Ja <input type="checkbox"/> Teils Nein / Teils Ja	<ul style="list-style-type: none"> <li>• Einfügen in den Erwachsenen-Impfkalender ist möglich</li> <li>• Ko-Administration mit nicht-adjuvantiertem inaktiviertem Influenza-Impfstoff an verschiedenen Körperstellen ist möglich (22)</li> </ul>	Weitere Studien zur Ko-Administration PCV13) sind abgeschlossen, aber noch nicht in der FI berücksichtigt oder sind noch nicht abgeschlossen (Tdap)



Empfehlung	Sollen alle Erwachsenen ab einem Alter von 65 Jahren mit einem Subunit-Impfstoff gegen HZ geimpft werden?				
<b>Abwägen der Folgen</b> <b>Balance of consequences</b>	unerwünschte Folgen überwiegen klar gegenüber den gewünschten	unerwünschte Folgen überwiegen wahrscheinlich gegenüber den gewünschten	Unerwünschte und gewünschte Folgen sind im Gleichgewicht oder die Balance ist unklar	gewünschte Folgen überwiegen wahrscheinlich gegenüber den unerwünschten	gewünschte Folgen überwiegen klar gegenüber den unerwünschten
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<b>Empfehlung</b>	<ul style="list-style-type: none"> <li>• Impfung aller Erwachsener ab einem Alter von <b>60 Jahren</b> mit einem Sub-Unit Impfstoff gegen HZ und PHN</li> </ul>				
<b>Begründung</b>	<p>Diese Empfehlung berücksichtigt die gute Wirksamkeit und das Sicherheitsprofil des Impfstoffes, die zu erwartende Schutzdauer bei seiner Anwendung sowie das zunehmende Risiko für schwere Krankheitsverläufe des Herpes zoster und für Postzosterschmerzen bei Personen im Alter von 60 Jahren und älter sowie Ergebnisse der epidemiologischen und gesundheitsökonomischen Modellierung.</p>				
<b>Berücksichtigung spezieller (Unter)Gruppen</b>	<p>Patienten mit eingeschränktem Immunsystem profitieren aufgrund ihres erhöhten Risikos für einen HZ im besonderem Maße von der Impfempfehlung; eine Alterserweiterung für bestimmte Indikationsgruppen entsprechend der Zulassung (ab 50 Jahre) kann deswegen erwogen werden</p>				
<b>Betrachtung zur Einführung / Umsetzung</b>	<ul style="list-style-type: none"> <li>• Impftermine für die Influenza-Impfung können mitgenutzt werden</li> <li>• Ko-Administration mit Influenza-Impfstoff ist möglich</li> </ul>				
<b>Monitoring and Evaluation</b>	<ul style="list-style-type: none"> <li>• Daten der KV Impfsurveillance stehen für die Impfquoten-Bestimmung der HZ Impfung bei Erwachsenen aller Altersgruppen zur Verfügung</li> <li>• Daten der KV Impfsurveillance sowie Meldedaten aus zwei Bundesländern zur Evaluation der Empfehlung (Impact-Analysen: vorher / nachher- Analysen: tritt erwartete Reduktion von HZ / PHN – Häufigkeit nach Einführung der Impfung auch wirklich ein?)</li> <li>• Individuelle Verlaufsdaten der KV-Impfsurveillance zur Berechnung der Impfeffektivität</li> <li>• Erfassung von Hintergrundinzidenzen zu ausgewählten Diagnosen (insbes. Autoimmunerkrankungen) durch KV-Impfsurveillance und PEI vor Impfeinführung und Vergleich zu Beobachtungen nach Impfempfehlung (expected vs. observed Analysen)</li> <li>• Passive Surveillance (PEI) bez. Sicherheit und unerwünschter Nebenwirkungen</li> </ul>				
<b>Forschungsprioritäten</b>	<ul style="list-style-type: none"> <li>• Fortlaufende Evaluation der Empfehlung und ihrer Umsetzung (Impact)</li> <li>• Impfeffektivität und Wirkdauer der Impfung (mit klinischen Endpunkten)</li> <li>• Fortlaufendes Monitoring der Impfstoffsicherheit (neues Adjuvanz)</li> </ul>				

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