# Grading of Recommendations Assessment, Development and Evaluation (GRADE): herpes zoster subunit vaccine

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# GRADE Process

- Develop policy questions
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category

# Policy Question: Should Herpes Zoster subunit vaccine (HZ/su) be routinely used to prevent herpes zoster?

| | |
|---|---|
| **Population** | Immunocompetent adults aged 50 years or older |
| **Intervention** | 2 doses of HZ/su (50 µg gE/$AS01_B$) administered intramuscularly at 0 and 2 months |
| **Comparison** | Placebo or no vaccine |
| **Outcomes** | Herpes zoster (HZ)<br>Post herpetic neuralgia (PHN)<br>Duration of protection against herpes zoster<br>Severe adverse events<br>Reactogenicity [Grade 3 rxn] |

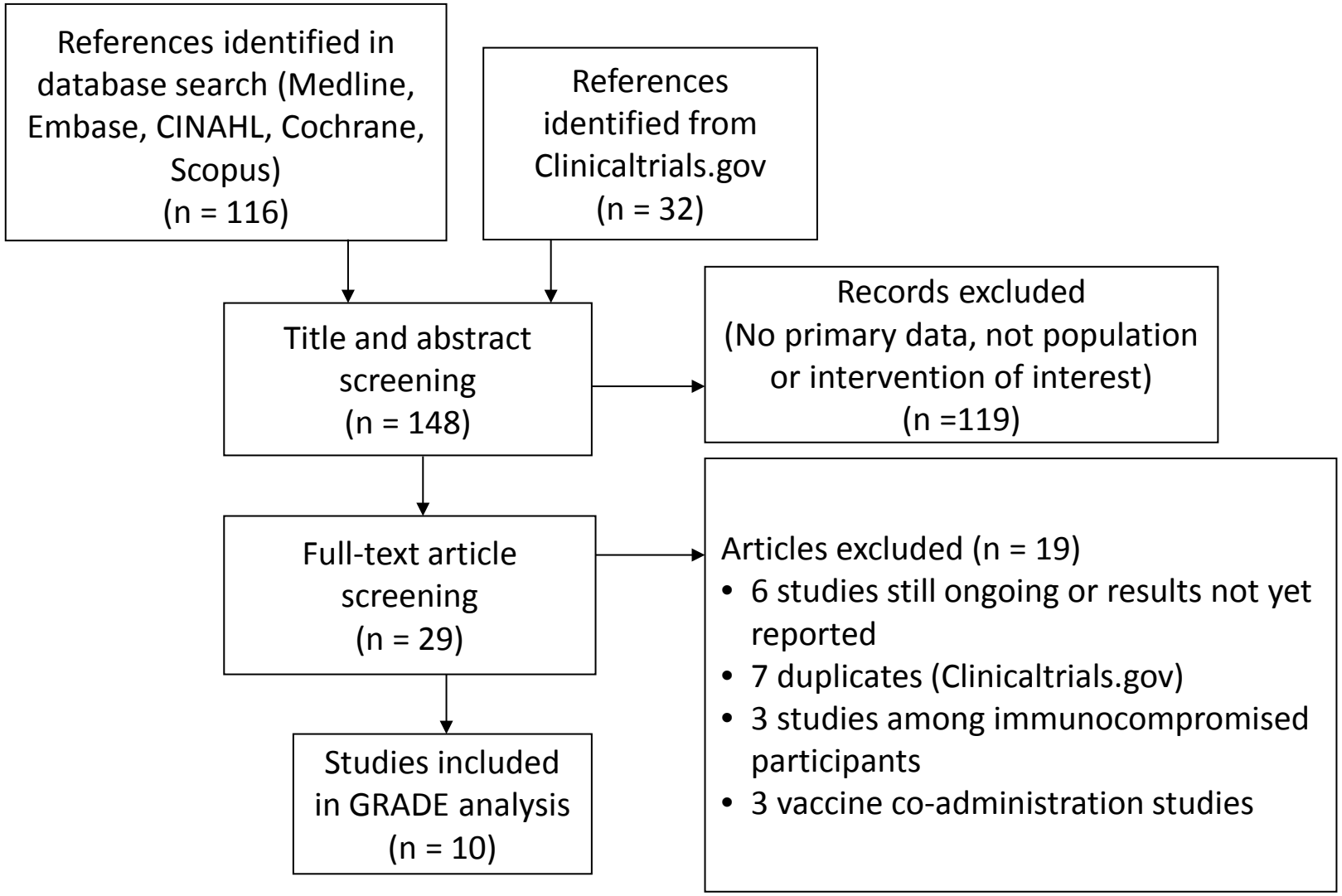
# Outcome measures included in evidence profile

| OUTCOME | IMPORTANCE |
|---|---|
| **Benefits** | |
| Prevent herpes zoster | Critical |
| Prevent postherpetic neuralgia | Critical |
| Duration of protection | Important |
| **Harms** | |
| Serious adverse events | Critical |
| Reactogenicity (Grade 3 rxn) | Important |

# Evidence Retrieval

- Systematic review of studies from PubMed, Embase, CINAHL, Cochrane, Scopus, and clinicaltrials.gov in any language
- Efforts made to obtain unpublished or other relevant data
- Initial search terms included: “herpes zoster” and “subunit,” or “HZ su ADJ5 subunit,” or “HZ su,” or “GSK 1437173A”
- Articles were included if they presented data on the herpes zoster subunit vaccine (HZ/su) and
  - Involved immunocompetent adults aged 50 years or older
  - Included data for a relevant intervention (50 µg gE/AS01$_B$, 2 doses at 0 and 2 months, intramuscularly)
  - Included data relevant to the outcome measures being assessed
  - Reported primary data

# Evidence Retrieval



# Evidence types

| Initial Evidence Type | Study Design |
|---|---|
| 1 | Randomized controlled trials (RCTs) or overwhelming evidence from observational studies |
| 2 | RCTs with important limitations, or exceptionally strong evidence from observational studies |
| 3 | Observational studies, or RCTs with notable limitations |
| 4 | Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations |

# GRADE of Evidence for HZ/su: Benefits

# Outcome #1: Incidence of herpes zoster
# Characteristics of included studies

| Study | Type | Population | Intervention | Comparison | Main outcomes | Funding | Site |
|---|---|---|---|---|---|---|---|
| Lal, NEJM, 2015 (ZOE-50) | RCT | Adults ≥50 yrs | HZ/su | Placebo | Vaccine efficacy for herpes zoster | GSK | 18 countries in Europe, North America, Latin America, and Asia–Australia |
| Cunningham, NEJM, 2016 (ZOE-50, ZOE-70) | RCT | Adults ≥70 yrs | HZ/su | Placebo | Vaccine efficacy for herpes zoster | GSK | 18 countries in Europe, North America, Latin America, and Asia–Australia |

# Outcome #1: Incidence of herpes zoster (HZ) Estimates of effect

| Outcome | No. of subjects (# studies) | Rate in controls (cases per 1000 person-yr) | Rate in vaccinated (cases per 1000 person-yr) | Vaccine efficacy (95% CI) |
|---|---|---|---|---|
| Herpes zoster, adults 50-59 y | 7017 (1) | 7.8 | 0.3 | 96.6 (89.6, 99.3) |
| Herpes zoster, adults 60-69 y | 4307 (1) | 10.8 | 0.3 | 97.4 (90.1, 99.7) |
| Herpes zoster, adults ≥ 70 y | 16,596 (1) | 9.3 | 0.8 | 91.3 (86.8, 94.5) |

# Outcome #1: Incidence of herpes zoster
# Type of Evidence

| Outcome | Design (# of studies) | Initial evidence level | Risk of bias | Inconsistency | Indirectness | Imprecision | Other consider-ations | Evidence type |
|---|---|---|---|---|---|---|---|---|
| Prevention of herpes zoster | RCT (1) | 1 | No serious | N/A | No serious | No serious | None | 1 |

# Outcome #2: Incidence of post-herpetic neuralgia (PHN) Characteristics of included studies

| Study | Type | Population | Intervention | Comparison | Main outcomes | Funding | Site |
|---|---|---|---|---|---|---|---|
| Cunningham, NEJM, 2016 (ZOE-50 & ZOE-70) | RCT | Adults ≥50 yrs | HZ/su | Placebo | Vaccine efficacy for PHN | GSK | 18 countries in Europe, North America, Latin America, and Asia–Australia |

# Outcome #2: Incidence of PHN
# Estimates of effect

| Outcome | No. of subjects (# studies) | Rate in controls (cases per 1000 person-yr) | Rate in vaccinated (cases per 1000 person-yr) | Vaccine efficacy (95% CI) |
|---|---|---|---|---|
| PHN, adults ≥ 50y | 27,916 (1) | 0.9 | 0.1 | 91.2 (75.9-97.7) |
| 50-59 y | 7014 (1) | 0.6 | 0.0 | 100.0 (40.8, 100.0) |
| 60-69 y | 4306 (1) | 0.2 | 0.0 | 100.0 (-442.9, 100.0) |
| PHN, adults ≥ 70y | 16,596 (1) | 1.2 | 0.1 | 88.8 (68.7-97.1) |

# Outcome #2: Incidence of PHN
# Type of Evidence

| Outcome | Design (# of studies) | Initial evidence level | Risk of bias | Inconsistency | Indirectness | Imprecision | Other consider-ations | Evidence type |
|---|---|---|---|---|---|---|---|---|
| Prevention of PHN | RCT (1) | 1 | No serious | N/A | No serious | No serious | None | 1 |

# Outcome #3: Duration of protection against herpes zoster Characteristics of included studies

| Study | Type | Population | Intervention | Comparison | Main outcomes | Funding | Site |
|---|---|---|---|---|---|---|---|
| Cunningham, NEJM, 2016 | RCT | Adults ≥70 yrs | HZ/su | Placebo | Vaccine efficacy for herpes zoster by year post vaccination | GSK | 18 countries in Europe, North America, Latin America, and Asia–Australia |

# Outcome #3: Duration of protection against herpes zoster Estimates of effect

| Time since vaccination | No. of subjects (# studies) | Rate in controls (cases per 1000 person-yr) | Rate in vaccinated (cases per 1000 person-yr) | Vaccine efficacy (95% CI) |
|---|---|---|---|---|
| **0 - 1 yr** | 16,596 (1) | 10.1 | 0.2 | 97.6 (90.9, 99.8) |
| **>1 - 2 yr** | 16,063 (1) | 11.1 | 0.9 | 92.0 (82.8, 96.9) |
| **>2 - 3 yr** | 15,397 (1) | 7.7 | 1.2 | 84.7 (69.0, 93.4) |
| **>3 - 4 yr** | 14,693 (1) | 8.2 | 1.0 | 87.9 (73.3, 95.4) |

# Outcome #3: Duration of protection against herpes zoster Type of Evidence

| Outcome | Design (# of studies) | Initial evidence level | Risk of bias | Inconsistency | Indirectness | Imprecision | Other consider-ations | Evidence type |
|---|---|---|---|---|---|---|---|---|
| Duration of protection | RCT (1) | 1 | No serious | N/A | No serious | No serious | None | 1 |

# GRADE of Evidence for HZ/su: Harms

# Outcome #4 and #5: Serious adverse events and reactogenicity
# Characteristics of included studies

| Study | Type | Population | Intervention | Comparison | Main outcomes | Funding | Site |
|---|---|---|---|---|---|---|---|
| Cunningham, *NEJM*, 2016 | RCT | Adults ≥70 yrs | HZ/su | Placebo | SAEs, reactogenicity | GSK | 18 countries in Europe, North America, Latin America, and Asia–Australia |
| Lal, *NEJM*, 2015 | RCT | Adults ≥50 yrs | HZ/su | Placebo | SAEs, reactogenicity | GSK | 18 countries in Europe, North America, Latin America, and Asia–Australia |
| Chlibek, *JID*, 2013 | RCT | Adults ≥50 yrs | HZ/su | Placebo | SAEs, reactogenicity | GSK | Czech Republic, Spain, and USA |
| Chlibek, *Vaccine*, 2014 *(and 2016 follow-up study)* | RCT | Adults ≥60 yrs | HZ/su | Unadjuvanted vaccine | SAEs, reactogenicity | GSK | Czech Republic, Germany, The Netherlands, and Sweden |

# Outcome #4 and #5: Serious adverse events and reactogenicity Characteristics of included studies

| Study | Type | Population | Intervention | Comparison | Main outcomes | Funding | Site |
|---|---|---|---|---|---|---|---|
| Poder, *IDWeek*, 2016 | RCT | Adults ≥50 yrs | HZ/su | None | SAEs, reactogenicity | GSK | USA and Estonia |
| Leroux-Roels, *JID*, 2012 | RCT | Adults 50-70 yrs | HZ/su | None | SAEs, reactogenicity | GSK | Belgium |
| Vink, *Hum. Vaccin. Immunother.*, 2016 | RCT | Adults ≥50 yrs | HZ/su | None | SAEs, reactogenicity | GSK | Japan |
| Godeaux, *Hum. Vaccin. Immunother.*, 2017 | Non-RCT | Adults ≥50 yrs | HZ/su | None | SAEs, reactogenicity | GSK | Canada and Russian Federation |
| Lal, *Hum. Vaccin. Immunother.*, 2013 | Non-RCT | Adults 50-69 yrs | HZ/su | None | SAEs, reactogenicity | GSK | Australia |

# Outcome #4: Serious adverse events
# Estimates of effect (ZOE-50 and ZOE-70)

| Outcome | No. of subjects (# studies) | No. reported in controls (%) | No. reported in vaccinated (%) | Difference |
|---|---|---|---|---|
| Serious adverse event* | 29,311 (1) | 1,900 (13.0%) | 1,842 (12.6%) | 0.4% |
| Serious adverse events considered related to vaccine** | 29,311 (1) | 15 (0.1%) | 15 (0.1%) | 0.0% |

- The remaining 7 studies administered HZ/su to a total of 616 participants and found no serious adverse events related to vaccination

**Throughout study period (mean follow up = 4 yrs)*
***ZOE-50: The three serious adverse events (SAE) considered to be related to vaccination by the investigators in the HZ/su group were immune thrombocytopenic purpura, musculoskeletal chest pain, and nervous system disorder.*
***ZOE-70: the SAEs considered by the investigator to be related to the trial intervention in the HZ/su group were lymphadenitis, acute myocardial infarction, ulcerative colitis, acute pancreatitis, administration-site erythema, administration-site pain, chills, pyrexia, allergic granulomatous angiitis, bacterial arthritis, erysipelas, herpes zoster oticus, eczema, neutropenic sepsis, and acute myeloid leukemia. Some participants had more than one event. One death in the HZ/su group was considered by the local investigator to be related to the vaccination.*

# Outcome #4: Serious adverse events
# Type of Evidence

- The four RCTs with no placebo group and the two non randomized trials were non-blinded, open-label trials and therefore, were downgraded for risk of bias and indirectness.
- Two non-randomized studies started at a lower initial evidence type.

| Outcome | Design (# of studies) | Initial evidence level | Risk of bias | Inconsist-ency | Indirect-ness | Imprecision | Other consider-ations | Evidence type | Outcome evidence type |
|---|---|---|---|---|---|---|---|---|---|
| Serious adverse events | RCT (2) | 1 | No serious | No serious | No serious | No serious | None | 1 | **1** |
| | RCT- no placebo (4) | 1 | Serious | No serious | Serious | No serious | None | 3 | |
| | Non-RCT (2) | 2 | Serious | No serious | Serious | No serious | None | 4 | |

# Outcome #5: Reactogenicity (Grade 3 rxn§) Estimates of effect (ZOE-50 and ZOE-70)

| Outcome | No. of subjects (# studies) | No. reported in controls (%) | No. reported in vaccinated (%) | Difference |
|---|---|---|---|---|
| Any Grade 3 reaction* | 9,936 (1) | 155 (3.1%) | 820 (16.5%) | 13.4% |
| Grade 3 injection-site reaction** | 9769 (1) | 17 (0.3%) | 460 (9.4%) | 9.1% |
| Grade 3 systemic reaction** | 9762 (1) | 116 (2.4%) | 528 (10.8%) | 8.4% |

§"Grade 3 injection site = redness and swelling at injection site >100 mm or preventing normal activity
Grade 3 systemic = temperature (oral) >39°C or preventing normal activity

**Solicited and unsolicited report of a Grade 3 reaction within 7 days after vaccination*
*** Solicited report of Grade 3 reaction within 7 days after vaccination*

# Outcome #5: Reactogenicity (Grade 3 rxn)
# Estimates of effect

- 4 additional studies reported any solicited grade 3 reactions after vaccination among participants who received HZ/su
  - 3.4%, (Godeaux, 2017, n=96)
  - 9.3%, (Chlibek, 2013, n=150)
  - 11.5%, (Poder, 2016, n=119)
  - 40%, (Lal, 2013, n=10)
- The remaining 3 studies that administered HZ/su to a total of 241 participants reported grade 3 reactions by symptom, and had findings consistent with reports of grade 3 reactions post vaccination in the previously stated studies

# Outcome #5: Reactogenicity (Grade 3 rxn)
# Type of Evidence

- The four RCTs with no placebo group were non-blinded, open-label trials and were downgraded for risk of bias and indirectness
- The two non-randomized studies had an initial evidence level of '2' and were downgraded for risk of bias and indirectness

| Outcome | Design (# of studies) | Initial evidence level | Risk of bias | Inconsist -ency | Indirect -ness | Imprecision | Other consider -ations | Evidence type | Outcome evidence type |
|---|---|---|---|---|---|---|---|---|---|
| Reactogenicity (Grade 3 rxn) | RCT (2) | 1 | No serious | No serious | No serious | No serious | None | 1 | 1 |
| | RCT- no placebo (4) | 1 | Serious | No serious | Serious | No serious | None | 3 | |
| | Non-RCT (2) | 2 | Serious | No Serious | Serious | No serious | None | 4 | |

# Summary

# ZOE-50 & ZOE-70 Limitations

- Reactogenicity of the vaccine may have resulted in effective un-blinding of some vaccine recipients, leading to opportunities for bias in reporting of adverse events and case ascertainment.

- Generalizability
  - Only 18% of participants were from North America and only 1% black participants
  - Study excluded those with a history of HZ, previous Zostavax recipients, and those taking immunosuppressant or immuno-modifying drugs

# GRADE Summary

## Comparison: 2 doses of HZ/su (50 µg gE/AS01B) versus placebo in adults ≥50

| Outcome | Design (# of studies) | Findings | Evidence type | Overall evidence type |
|---|---|---|---|---|
| **CRITICAL** | | | | |
| Prevent herpes zoster | RCT (1) | HZ/su significantly efficacious in preventing herpes zoster | **1** | **1** |
| Prevent post-herpetic neuralgia | RCT (1) | HZ/su significantly efficacious in preventing PHN | **1** | |
| Severe adverse events | RCT (2)<br>RCT* (4)<br>Non-RCT (2) | No differences detected between vaccinated and comparison populations for serious adverse events | **1** | |
| **IMPORTANT** | | | | |
| Reactogenicity (Grade 3 rxn) | RCT (2)<br>RCT* (4)<br>Non-RCT (2) | Grade 3 reactions more commonly reported in vaccinated groups compared to placebo | 1 | |
| Duration of protection (herpes zoster) | RCT (1) | HZ/su significantly efficacious in preventing herpes zoster 4 years post last vaccination | 1 | |

# Considerations for formulating recommendations for use

# Herpes Zoster and Post Herpetic Neuralgia epidemiology, United States

- Annual rate ~4 cases per 1000 population (1 million cases annually)[1,2]
- Incidence increases with age, ranging from <1 case/1000 children to >15 cases/1000 population 80 years and older[2,3]
- For adults 50 years and older with HZ, 10-18% will go on to develop PHN. Similar to HZ, the incidence increases with age[3]
- Incidence of HZ is decreasing in children, increasing in younger adults and has plateaued in adults ≥65 yrs[4]


1. **Jumaan et al., JID, 2005, 191:2002-7**
2. **Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9**
3. **Insinga et al., J Gen Intern Med. 2005, 20:748-53**
4. **Hapaz et al, IDWeek 2015**

# Current Herpes Zoster Vaccination, United States

- Zostavax, a live attenuated vaccine for the prevention of HZ, was recommended by ACIP in 2008 for immunocompetent adults ≥60 yrs
- Vaccine efficacy: 51% against HZ and 67% against PHN[5]
- Duration of protection against HZ[5,6]
  - Year 1: 62%
  - Year 4: 45%
  - Year 9: 7%
- Adverse Events Following Immunization[5]
  - Serious adverse events: no significant difference between placebo and vaccine
  - Any adverse event:  34% placebo vs. 58% vaccine
- 31% of adults ≥60 yrs have been vaccinated with Zostavax[7]

5. Oxman et al. 2005, NEJM
6. Morrison et al. 2015, CID
7. CDC 2015 Adult Vaccination Coverage General Population Report: https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/coverage-estimates/2015.html

# Considerations for formulating policy recommendations: HZ/su in immunocompetent older adults

| Key Factors | Comments |
|---|---|
| Evidence type for benefits and harms | • Prevention of HZ and PHN: **Evidence type 1**<br>• Occurrence of serious adverse events: **Evidence type 1** |
| Balance between benefits and harms | • HZ and PHN were significantly less frequent in the vaccinated group<br>• HZ was significantly less frequent in the vaccinated group 4 years following vaccination<br>• Serious adverse events occurred at similar rates in vaccinated and placebo groups<br>• Grade 3 reactions occurred more frequently in vaccine recipients<br>• **Benefits outweigh harms** |
| Values | • ACIP HZ Work Group placed **high value** on prevention of HZ and PHN<br>• Community members placed **high value** on prevention of HZ and PHN[8]<br>• Patients who had experienced herpes zoster consistently placed the **highest value** on avoidance of the disease[8] |
| Cost-effectiveness | To be determined |

8. Lieu, Pharmacoeconomics 2009

# Information gaps for policy making

- What will 2 dose compliance be under real world conditions?
  - Will non-completion of the series have an effect on vaccine effectiveness?
  - Will non-completion of the series have an effect on duration of protection?
- What protection can HZ/su provide beyond 4 years?
- No data yet available to assess vaccine efficacy in immunocompromised persons
  - Phase III trials of 2 vaccines (HZ/su and V212) ongoing.
  - Efficacy and safety data from these trials will inform vaccine policy in this high risk group
- No head to head comparisons of vaccine efficacy between HZ/su and Zostavax

# Work Group deliberations on the use of HZ/su

- Based on review of the evidence for critical and important outcomes, the Work Group's interpretation is that the vaccine is safe, efficacious and maintains high protection against HZ four years following vaccination among immunocompetent adults aged 50 years and older

<u>Under active consideration:</u>

- Recommend routine vaccination at age 50 vs. age 60?
- Should persons previously vaccinated with Zostavax be revaccinated with HZ/su?
- What vaccine policy would prevent the greatest burden of HZ and PHN if 2 licensed vaccines are available for use?
- What is the most cost effective vaccine program?

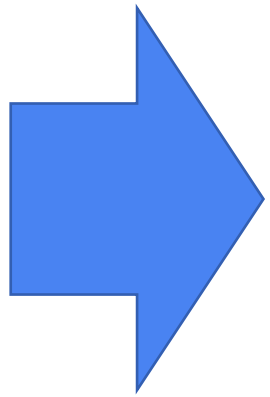
# Next steps

- Analysis
  - Cost effectiveness analysis for HZ/su in the context of the current vaccine program
  - GRADE for Zostavax

- Forthcoming data for consideration
  - Co-administration of HZ/su with other adult vaccines and expanded dosing schedules
  - Immunogenicity and safety in adults who have previously received Zostavax
  - Immunogenicity and safety in Zostavax vs HZ/su

# Discussion

| FEB 2017 | JUN 2017 | OCT 2017 |
| --- | --- | --- |
| • HZ/su safety & long term imm.<br>• HZ/su GRADE | • Zostavax GRADE<br>• HZ/su/Zostavax imm.<br>• Cost effectiveness<br>• Considerations for policy | • GRADE summary<br>• Cost effect. summary<br>• Considerations |



**VOTE**

**Are there additional data that would be helpful to ACIP to inform a recommendation for the use of HZ/su in immunocompetent adults?**