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A systematic approach for immunization decision-making.

--Experiences from Germany (STIKO)--

Ole Wichmann

Subregional meeting of National Immunization Programme Managers in the WHO European Region, Izmir, Türkiye, 3-4 May, 2023

Immunisation system in Germany

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- Decentralized healthcare system
  - under the responsibility of 16 federal states
  - but: one national vaccination schedule according to STIKO (German NITAG)
- “Private vaccine market”
  - procurement/distribution through wholesalers
  - delivery mainly through private physicians
- Funding through health insurance funds
  - by law, all STIKO-recommended vaccines must be reimbursed by insurance companies
  - vaccines not recommended can be voluntarily reimbursed or paid out-of-pocket
- STIKO recommendations are the basis for
  - directive for reimbursement (responsible: Joint Federal Committee)
  - vaccine injury compensation program (responsible: federal states)

Vaccine introduction decisions

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Decisions involves trade-off between likely benefits and downsides (risks) both **at individual and population level**

- Likely benefits: e.g.
  - reduction in number of cases, hospitalizations, deaths
  - protection of unvaccinated persons (by herd effects)
  - decreased costs in the healthcare system
  - elimination/eradication of a disease
- Likely downsides: e.g.
  - adverse events following immunization
  - serotype replacements / shift in age-distribution at population level
  - program costs

STIKO‘s process in implementing a systematic approach / evidence-based medicine (EBM)

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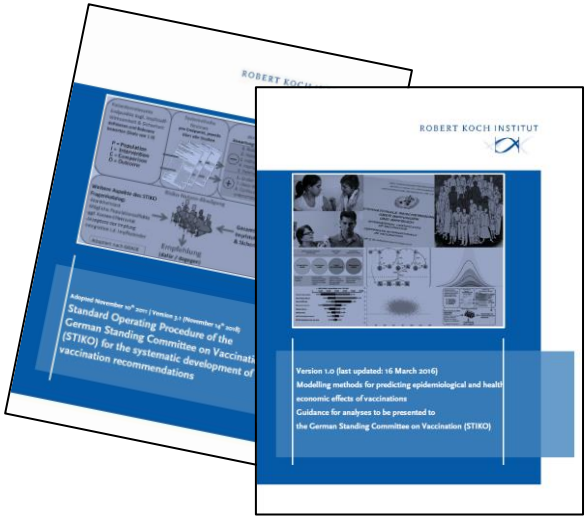

www.stiko.de/en

- **2008:** Established working group on methods
- **2010-11:** Two international meetings in Berlin
- **2011:** Decision to test applicability of GRADE
  - training of STIKO secretariat & members
- **2012:** Standard Operating Procedures (SOP)
- **2012:** RKI employs full-time EBM specialist
- **2015:** Evidence-to-recommendation (EtD) tool
- **2016:** Methods paper for transmission & health economic modelling
  - informed by an international expert & national stakeholder meeting

Content of STIKO‘s SOP

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1. Topic selection and prioritization
2. Involved groups and tasks
3. Key questions to be addressed
4. Formulation of the vaccination goal
5. Development of PICO questions
6. Systematic literature review
7. Identification of relevant studies
8. Data extraction, evaluation of individual studies
9. Information synthesis
10. Synthesis of results and decision-making
11. Publication
12. Appendices (examples of extraction sheet, GRADE evidence profile, EtR-table)

Online at: www.stiko.de/en

Key questions according to SOP

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1. **Pathogen**
   -e.g. pathogen characteristics, sub-type distribution
2. **Target disease**
   -disease incidence/burden/epidemiology/case fatality/risk groups
3. **Vaccine characteristics**
   -effectiveness/immunogenicity, safety, duration of protection, contraindication
4. **Immunization strategy**
   -immunization goal, number-needed-to-vaccinate
   -expected (population-level) effects based on models
   -health economic impact
   -ethical implications
5. **Implementation of recommendation**
   -integration into existing schedule
   -expected vaccine acceptance
   -monitoring systems, missing data / research needs

GRADE

Outcomes

define & **ranking**

Patient relevant outcomes (vaccine efficacy & safety)

→ critical

→ critical

→ important

↘ Less important

P = Population
I = Intervention
C = Comparison
O = Outcome

Systematic Review
(Outcomes across all studies)

GRADE-ing („body of evidence")

RCT initially high,
Epi-studies initally low

Down: 1. Risk of bias
2. Inconsistancy
3. Indirectness
4. Imprecision
5. Publication Bias

Up: 6. Strong effect
7. Dose-response
8. Confounder

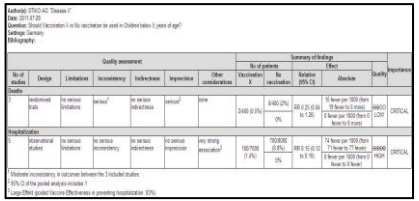
For each outcome final evidence level:
-High
-Moderate
-Low
-Very low

Other key question from STIKO SOP:
-Disease burden / epidemiology
-Expected impact
-costs / cost-effectiveness
-Acceptance of vaccination
-Integration into schedule

→

Risik-benefit-assessment

←



Vaccine efficacy & safety:
Evidence level based on lowest level of critical outcomes

↓

Recommendation

(for / against)

Adapted from GRADE

Advantages of using GRADE

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- Widely applied methodology (e.g. WHO, US-ACIP, German STIKO)
- Separation of the two steps (!)
  - grading quality of evidence
  - from evidence to recommendation
- For assessing quality of evidence
  - evidence from RCTs and observational studies
  - focus on effect outcomes of intervention (efficacy, effectiveness, safety) = “context-free”
- For recommendation development
  - additional “context-specific” aspects (e.g. disease incidence, values/preferences, cost-effectiveness) possible

Principles of „setting limits fairly“

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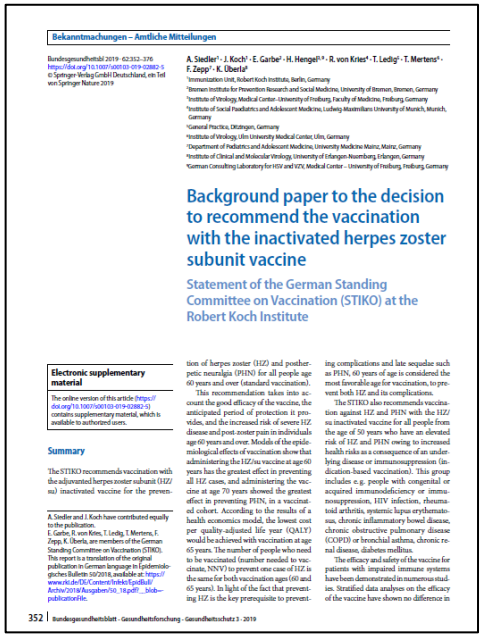
- **Transparency**
  - all relevant documents published online, GRADE, EtR-tables
- **Justification**
  - scientific rationale & background paper to be published
- **Open for revision**
- **Consistency**
  - framework established and published (SOP)
- **Participation**
  - external review by professional societies, federal states, Joint Federal Committee (incl. patient representative)
- **Minimizing conflict of interest**
  - strict procedures in place

Example:
Vaccination against Herpes Zoster

Recommendation of the inactivated HZ-subunit vaccine

- Standard vaccination for all persons aged ≥ 60 years
- Risk-groups (elevated HZ risk due to underlying diseases or immunodeficiency) aged ≥ 50 years



Bekanntmachungen – Amtliche Mitteilungen

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Background paper to the decision to recommend the vaccination with the inactivated herpes zoster subunit vaccine

Statement of the German Standing Committee on Vaccination (STIKO) at the Robert Koch Institute

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00103-019-02882-5) contains supplementary material, which is available to authorized users.

Summary

The STIKO recommends vaccination with the adjuvanted herpes zoster subunit (HZ/su) inactivated vaccine for the preven-

A. Stedler and J. Koch have contributed equally to the publication.
E. Garbe, R. von Kries, T. Ledig, T. Mertens, F. Zepp, K. Überla, are members of the German Standing Committee on Vaccination (STIKO).
This report is a translation of the original publication in German language in Epidemiologisches Bulletin 50/2018, available at: https://www.rki.de/DE/Content/Infekt/EpiBull/Archiv/2018/Ausgaben/50_18.pdf?__blob=publicationFile.

tion of herpes zoster (HZ) and postherpetic neuralgia (PHN) for all people age 60 years and over (standard vaccination).

This recommendation takes into account the good efficacy of the vaccine, the anticipated period of protection it provides, and the increased risk of severe HZ disease and post-zoster pain in individuals age 60 years and over. Models of the epidemiological effects of vaccination show that administering the HZ/su vaccine at age 60 years has the greatest effect in preventing all HZ cases, and administering the vaccine at age 70 years showed the greatest effect in preventing PHN, in a vaccinated cohort. According to the results of a health economics model, the lowest cost per quality-adjusted life year (QALY) would be achieved with vaccination at age 65 years. The number of people who need to be vaccinated (number needed to vaccinate; NNV) to prevent one case of HZ is the same for both vaccination ages (60 and 65 years). In light of the fact that preventing HZ is the key prerequisite to preventing complications and late sequelae such as PHN, 60 years of age is considered the most favorable age for vaccination, to prevent both HZ and its complications.

The STIKO also recommends vaccination against HZ and PHN with the HZ/su inactivated vaccine for all people from the age of 50 years who have an elevated risk of HZ and PHN owing to increased health risks as a consequence of an underlying disease or immunosuppression (indication-based vaccination). This group includes e.g. people with congenital or acquired immunodeficiency or immunosuppression, HIV infection, rheumatoid arthritis, systemic lupus erythematosus, chronic inflammatory bowel disease, chronic obstructive pulmonary disease (COPD) or bronchial asthma, chronic renal disease, diabetes mellitus.

The efficacy and safety of the vaccine for patients with impaired immune systems have been demonstrated in numerous studies. Stratified data analyses on the efficacy of the vaccine have shown no difference in

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https://link.springer.com/article/10.1007/s00103-019-02882-5

Policy question and vaccination goal

Policy Question:
Should the inactivated Herpes zoster (HZ)-subunit vaccine
be recommended as standard vaccination for the prevention of HZ?

Goal of vaccination:
Reduction of burden of HZ disease and its complications

Evidence-to-recommendation (EtR) tables

STIKO - Herpes Zoster vaccination

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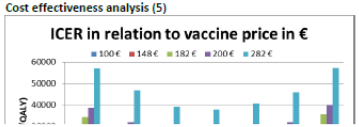
	Criteria	Judgments	Research evidence	Additional considerations
Problem	Is the problem a priority?	☐ No ☐ Probably no	HZ-incidence in Germany (1, 2): • 6 HZ/ 1,000 inhabitants (women >men) • <50 years: 4 HZ/1,000 person-years (PY)[5]	Burden of HZ increases with age, steep increase occurring after at the age of 50 to 70 years; at the

	Criteria	Judgments	Research evidence	Additional considerations
Benefits & Harms of the option	Are the desirable anticipated effects large?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes	Vaccine efficacy (VE) (systematic review) (3, 4): - Prevention of HZ (50+ years): 92% (89.9 – 94.0) - Age-group 50-59: 97% (90.0 – 99.0) - Age-group 60-69: 94% (85.0 – 98.0) - Age-group 70-79: 90% (85.0 – 93.0)	Small decrease of VE with higher age, VE remains above 89% in all age groups Vaccination effectiveness relatively

	Criteria	Judgments	Research evidence	Additional considerations
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably no ☐ Uncertain ☒ Probably yes ☐ Yes	Cost effectiveness analysis (5) 	(ICERs not yet adjusted to the real vaccine price - this will be between 200 and 282€; thus the ICERs in relation to vaccination age will still change in value but not in tendency!)

		Criteria	Judgments	Research evidence			Additional considerations
			☒ Moderate ☐ High	Vaccine related SAE Potential immune mediated disease	CRITICAL CRITICAL	MODERATE MODERATE	
Benefits & Harms of the option	Values	Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☒ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes	Observational studies demonstrated substantial impact of HZ and PHN on quality of life: daily activities, mobility, work, sleep, mood, social relations were negatively affected (15, 16) Majority of family members (69% children; 80% life partners) of patients with HZ or PHN said that caring for the patient resulted in a moderate to severe impact on their life (17) The perceived burden of disease is therefore certainly large. However, it remains unclear what influence this loss of quality of life will have on the use of vaccination.			High reactogenicity and / or unfavorable experience of the first vaccine dose could impair readiness for the 2nd vaccination
	Resource use	Are the resources required small?	☐ No ☐ Probably no ☒ Uncertain ☐ Probably yes ☐ Yes ☐ Varies	Vaccine costs: 113.40 € per dose and additional administration costs			Price not yet available

Is the problem a priority? -- YES

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HZ-incidence in Germany:

- Range: 6.2/1,000 PY (age 50-54 yrs) to 14 HZ/1,000 PY (age 80-89 yrs).

Hospitalization discharge data (average 1995-2012):

- Range: 6.7 (age 20–49-yrs) to 57.7 (age ≥90 yrs) HZ/100,000 inhabitants

HZ incidence in persons with immunosuppression

- twice as high as in immunocompetent persons (12 vs. 6 HZ cases/1,000 PY).

HZ-related mortality:

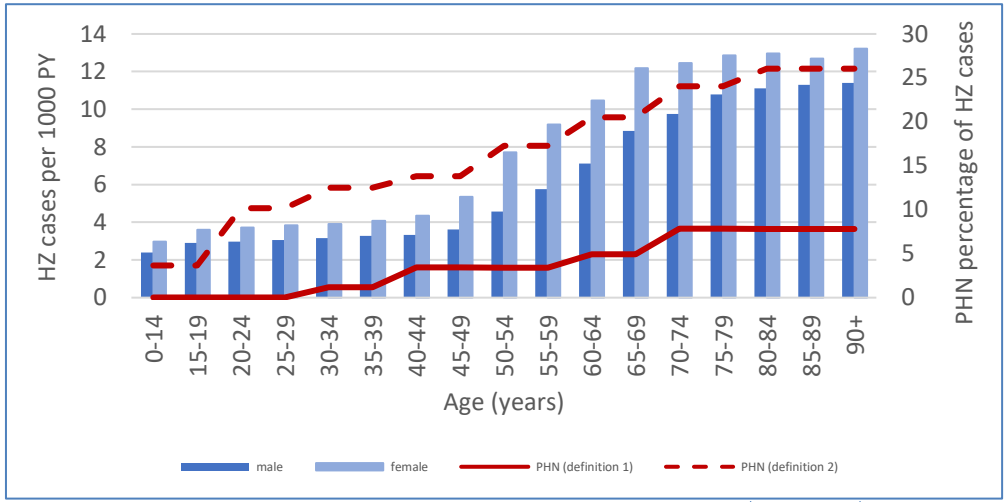
- ≥50 years: 75/year, 2005-2014

Post herpetic neuralgia (PHN)-incidence:

- 11.5% - 14.9% of HZ-cases develop PHN

HZ complications (except PHN) in 28%:

- Involvement of the nervous system (15.5%)
- Zoster ophthalmicus (4.8%)
- Disseminated zoster (0.6%)
- Zoster encephalitis (0.4%)
- Zoster meningitis (0.1%)



Benefits & Harms (I) - desirable anticipated effects **large**?

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Vaccine efficacy (VE) (systematic review):

Prevention of HZ (50+ years): 92% (89.9 – 94.0)

- Age-group 50-59: 97% (90.0 – 99.0)
- Age-group ≥80: 90% (79.0 – 95.0)

Prevention of PHN (50+ years): 82% (64.0 – 91.0)

- Age-group 50-59: 95% (9.0 – 100.0)
- Age-group 70-79: 87% (63.0 – 95.0)
- Age-group ≥80: 4% (-124.3 – 84)

Duration of protection: 4 years after immunization >85% in ≥70 year-olds

Static cohort Markov model:

Under the assumption of **35,5% vaccination coverage** the following effects can be achieved in a cohort of 1 million 50-year-olds to the end of their lives, when vaccine is administered at the age of 60 years:

- Prevention of 21,924 HZ- cases
- Prevention of 1,376 PHN-cases

Number needed to vaccinate (NNV), when immunized at age 60, 65, 70 yrs:

- NNV to prevent 1 HZ case: 15, 15, 16
- NNV to prevent 1 PHN-case: 244, 214, 197

Benefits & Harms (II) - undesirable anticipated effects **small?**

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Injection site reactions:

Frequency in the vaccine vs. placebo group (Grade 3):

- Injection site reaction: 58.2% vs. 4.9% (2.4 vs. 0.1%)
- Erythema: 28.2% vs. 0.6% (2.4 vs. 0.0%)
- Swelling: 15.4% vs. 0% (0.9 vs. 0.0%)
- Median duration: 2 - 3 days

Systemic reactions:

Frequency in the vaccine vs. placebo group (Grade 3):

- Fever: 7.8% vs. 1.5% (0.0 vs. 0.4%)
- Myalgia: 22.1% vs. 4.5% (1.3 vs. 0.2%)
- Headache: 14.9% vs. 0.7% (0.6 vs. 0.4%)
- Fatigue: 22.8% vs. 9.6% (1.7 vs. 0.4%)
- Median duration: 1 - 2 days

- No signal for potential immune-mediated diseases: 1.2% vs. 1.3%
- No signal for severe adverse events. 0.1% vs. 0.1%
- No vaccine related deaths

Benefits & Harms (III) - overall certainty of this evidence?

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- **Effectiveness of the intervention:** moderate
- **Safety of the intervention:** moderate

Outcome	Relative importance	GRADE
Effectiveness of the intervention		
Herpes Zoster	CRITICAL	High
PHN	CRITICAL	Low
Safety of the intervention		
Pain	CRITICAL	Moderate
Vaccine-related AE	IMPORTANT	High
Fever	CRITICAL	High
Vaccine-related SAE	CRITICAL	Moderate
Potential immune mediated disease	CRITICAL	Moderate

Values and resource use

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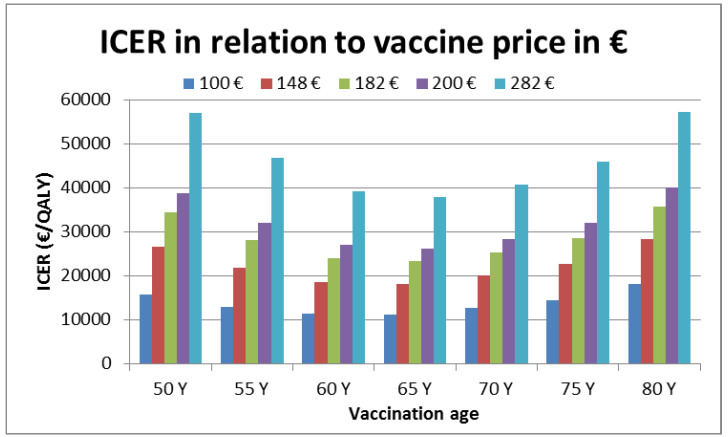
Values

- Observational studies demonstrated substantial impact of HZ and PHN on quality of life: daily activities, mobility, work, sleep, mood, social relations were negatively affected.
- Majority of family members (69% children; 80% life partners) of patients with HZ or PHN said that caring for the patient resulted in a moderate to severe impact on their life.

Resource use

- Vaccine price not yet available



Equity, Acceptability, Feasibility

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Equity

- uniform principles would apply (for those at increased risk) and the cost of vaccination would be borne by the statutory health insurance

Acceptability

- Individual choice is determined by knowledge about the disease and personal risk assessment
- Advice by general practitioner most important predictor for being vaccinated
- Other vaccines at age 60+ yrs: Seasonal Influenza (35%) & Pneumococcal (31%)

Feasibility

- Implementation possible into routine vaccination schedule for adults
- Coadministration with non-adjuvanted influenza vaccine possible

Recommendation

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Recommendation	**Should adults' ≥60 years of age be vaccinated with the inactivated HZ-subunit vaccine against HZ?**				
Balance of consequences	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	The balance between desirable and undesirable consequences is closely balanced or uncertain	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
	☐	☐	☐	☐	☒
Recommendation	• Vaccination of all adults at the **age ≥60 years** with the inactivated HZ-subunit vaccine against HZ and PHN				
Justification	This recommendation takes into account the good efficacy and safety profile of the vaccine, the expected duration of protection during its use and the increasing risk of severe herpes zoster and post zoster neuralgia in persons aged ≥ 60 years, as well as the results of epidemiological and health economic modelling.				
Subgroup considerations	Immunosuppressed patients can particularly benefit from the HZ-vaccine recommendation due to their increased risk of developing a HZ; an age extension for certain indication groups according to the approval (for those aged ≥ 50 years) can therefore be considered.				
Implementation considerations	• Influenza vaccine appointments can be used to perform HZ vaccinations • Coadministration with influenza vaccine possible				
Monitoring and evaluation	• Use of "KV Impfsurveillance" to measure HZ vaccination coverage in adults ≥60 years of age • Use of "KV Impfsurveillance" and Herpes zoster notification data from two federal states to evaluate the recommendation (Impact-Analysis: before and after analysis: Did the expected reduction of HZ and PHN occur after implementation of the recommendation for HZ/su vaccination • Case based analysis of "KV-Impfsurveillance" data to determine the vaccine effectiveness of the HZ/subunit vaccine				

Conclusions

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- Succesful application of a framework / systematic approach
  - helps to improve quality of the recommendation
  - improves transparency, facilitates critical appraisal and comparison
  - contributes to the acceptance in the professional community and the public
  - EtR tables summarize evidence and guide discussions in the committee

- Time- and resource-consuming
  - acceptable, since quality increased considerably
  - way to handle this, e.g.
    (a) utilize existing reviews as shortcuts (e.g. SYSVAC)
    (b) international collaboration (e.g. bilateral, EU NITAG network)
    (c) prioritization of topics
    (d) stay pragmatic