# Anhang zur wissenschaftlichen Begründung zur Empfehlung der STIKO zum Einsatz von Hochdosis- und MF-59-adjuvantierten Influenza-Impfstoffen bei der Standardimpfung von Personen ≥ 60 Jahre zum Schutz vor Erkrankungen durch Influenzaviren

## Inhaltsverzeichnis

## 1. PICO questions for the systematic review on the effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over

| | | | |
|---|---|---|---|
| **Population** | | Subject ≥ 18 years or older irrespective of health status or setting | |
| **Intervention** | | • MF-59 adjuvanted trivalent or quadrivalent inactivated vaccine<br>• high-dose trivalent or quadrivalent inactivated vaccine<br>• cell-based trivalent or quadrivalent inactivated vaccine<br>• recombinant trivalent or quadrivalent HA vaccine<br>• quadrivalent mRNA-based vaccine | |
| **Comparison** | | any seasonal influenza vaccine (head-to-head comparisons), including conventional as well as new/enhanced influenza vaccines | |
| **Outcomes** | **Effectiveness** | | **Importance** |
| | | Laboratory-confirmed influenza (laboratory-confirmed) | Critical |
| | | Influenza-related hospitalization (laboratory-confirmed) | Critical |
| | | Influenza-related death (laboratory-confirmed) | Critical |
| | | Influenza-associated cardiovascular disease (laboratory-confirmed) | Important |
| | | Influenza associated pneumonia/lower respiratory tract disease (laboratory-confirmed) | Important |
| | | Influenza-like illness (ILI) Internationally accepted case definitions to be used (e.g. WHO, US CDC, EU) | Important |
| | **Safety** | Serious adverse events | Critical |
| | | Inflammatory neurologic events | Important |
| | | Reactogenicity (local and systemic events) | Important |

# 2. Search strategies for the Update of the systematic review on the effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over

## 2.1. MEDLINE and Embase via OVID

The complete search string can be found in the Annex 1 of the updated systematic Review of enhanced seasonal influenza vaccines for prevention of influenza in individuals aged 18+ years [1].

Webpage: https://www.ecdc.europa.eu/en/publications-data/systematic-review-update-efficacy-effectiveness-and-safety-newer-and-enhanced

# 3. PRISMA-Flowchart

PRISMA flow diagram of the update search on 24th July 2023 for the systematic review. Search period from 1st January 2020 to 24th July 2023.

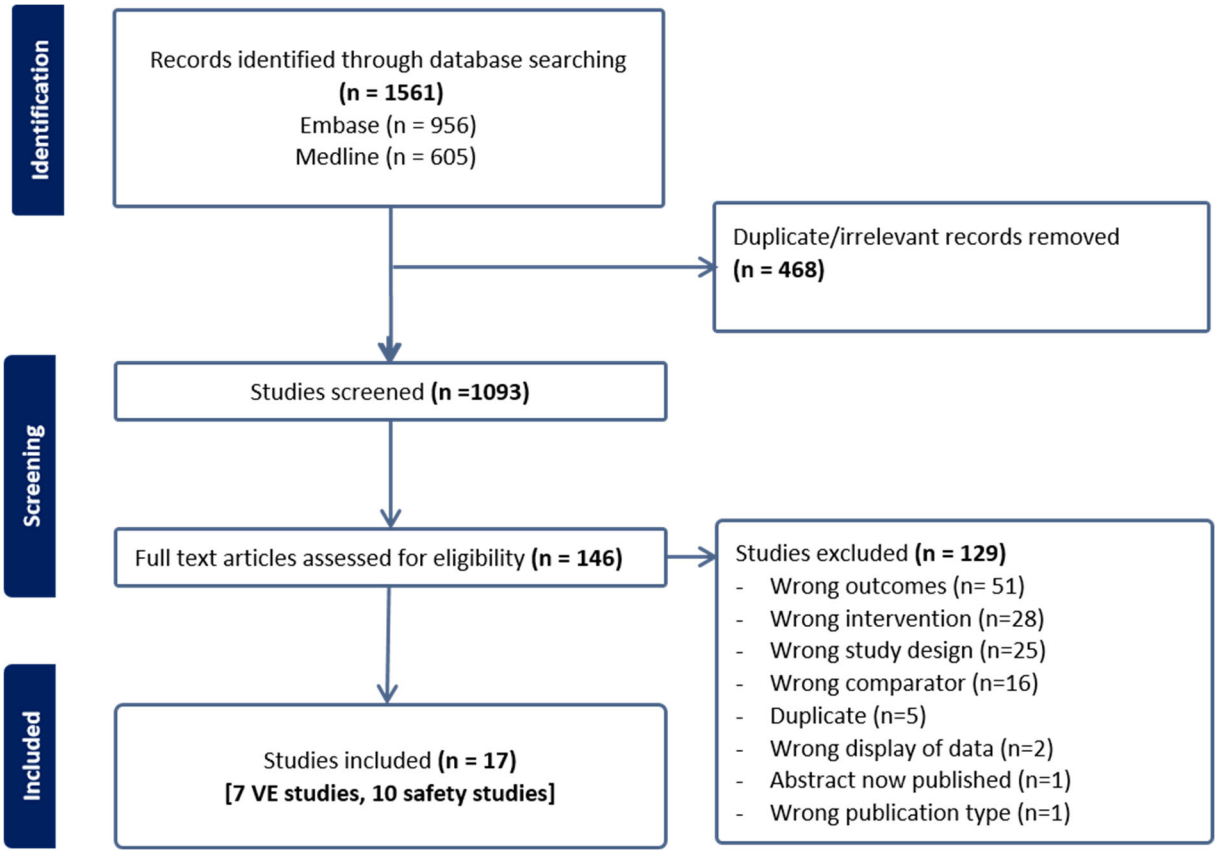


*Figure 1: Flow diagram of update search **24th of July 2023***

PRISMA flow diagram of the systematic search for further published evidence since publication of the updated systematic review. Search conducted on 2nd September 2024. Search period from 1 January 2020 to 2nd September 2024. Irrelevant studies included the removal of studies that were already identified in the search contacted on 24th of July 2023. The 472 studies represent new published data since that date. Two further studies were identified, which met the inclusion criteria of the systematic review [2].

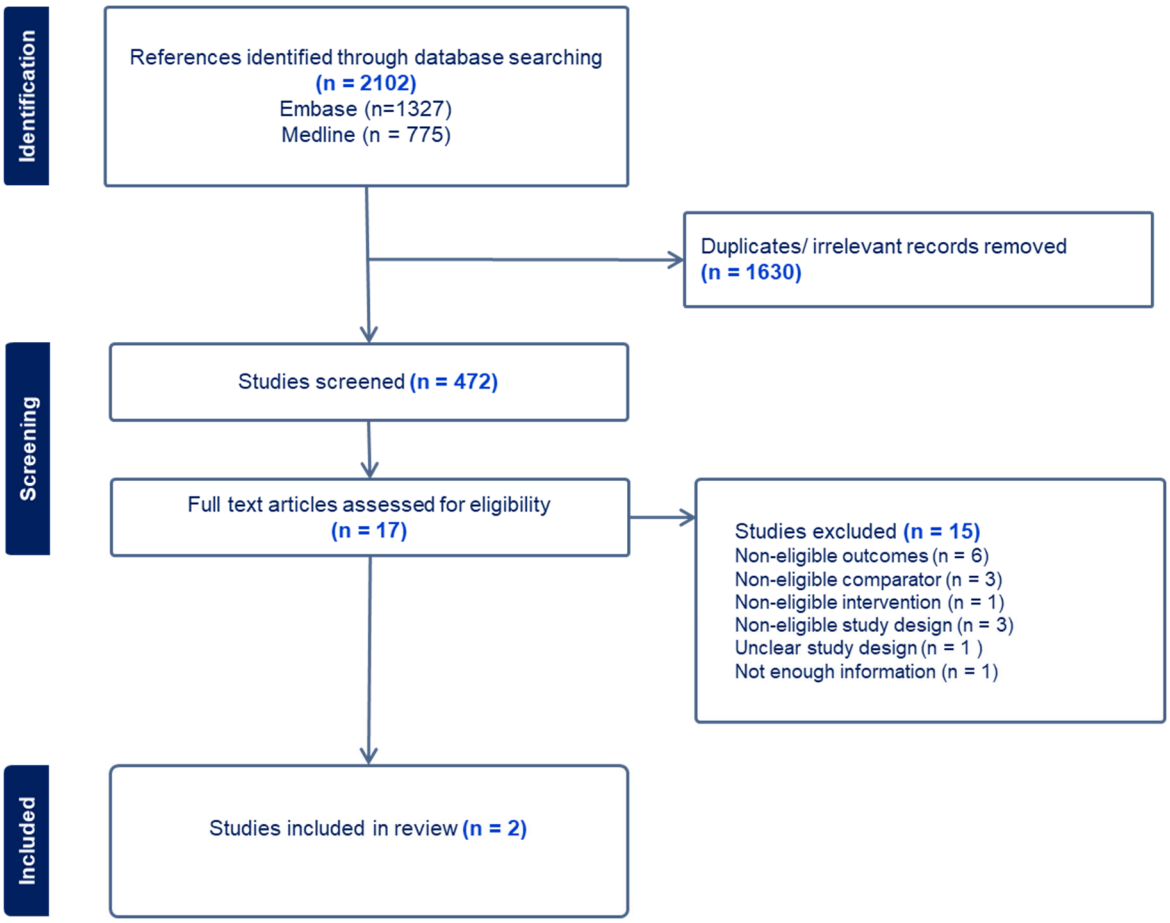


*Figure 2: Flow diagram of update search **2nd of September 2024***

## 4. List of excluded publications

List of excluded publications during full text screening of search conducted on 2nd September 2024. For excluded publications of the updated systematic review with the search conducted on 24th of July 2023 see ANNEX 2 of the published review [3].

**Non-eligible study design (n = 3)**

Gartner, B. C., Beier, D., Gosch, G., Wahle, K., Wendt, L., Forster, L.-C., . . . Schwarz, T. F. (2024). Cell-based influenza vaccines: An effective vaccine option for under 60-year-olds. *GMS hygiene and infection control, 19*, Doc21. doi:https://dx.doi.org/10.3205/dgkh000476

Martin, E. T., Cheng, C., Petrie, J. G., Alyanak, E., Gaglani, M., Middleton, D. B., . . . Ferdinands, J. M. (2021). Low Influenza Vaccine Effectiveness Against A(H3N2)-Associated Hospitalizations in 2016-2017 and 2017-2018 of the Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN). *The Journal of infectious diseases, 223*(12), 2062-2071. doi:https://dx.doi.org/10.1093/infdis/jiaa685

Domnich, A., Icardi, G., Panatto, D., Scarpaleggia, M., Trombetta, C.-S., Ogliastro, M., . . . Orsi, A. (2024). Influenza epidemiology and vaccine effectiveness during the 2023/2024 season in Italy: A test-negative case-control study. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*, 107202. doi:https://dx.doi.org/10.1016/j.ijid.2024.107202

**Non-eligible outcomes (n = 6)**

Johansen, N. D., Modin, D., Nealon, J., Samson, S., Salamand, C., Loiacono, M. M., . . . Biering-Sorensen, T. (2023). A Pragmatic Randomized Feasibility Trial of Influenza Vaccines. *NEJM evidence, 2*(2), EVIDoa2200206. doi:https://dx.doi.org/10.1056/EVIDoa2200206

Lassen, M., Johansen, N. D., Modin, D., Nealon, J., Loiacono, M., Jensen, A. M. R., . . . Biering-Sorensen, T. (2024). EFFECTS OF HIGH-DOSE VS. STANDARD-DOSE QUADRIVALENT INFLUENZA VACCINE AMONG PATIENTS WITH DIABETES: A POST-HOC ANALYSIS OF THE DANFLU-1 TRIAL. *Journal of the American College of Cardiology, 83*(13 Supplement), 1905. doi:https://dx.doi.org/10.1016/S0735-1097%2824%2903895-6

Palmu, A. A., Pepin, S., Syrjanen, R. K., Mari, K., MallettMoore, T., Jokinen, J., . . . DeBruijn, I. (2024). High-Dose Quadrivalent Influenza Vaccine for Prevention of Cardiovascular and Respiratory Hospitalizations in Older Adults. *Influenza and other respiratory viruses, 18*(4), e13270. doi:https://dx.doi.org/10.1111/irv.13270

Seppala, E., Dahl, J., Veneti, L., Rydland, K. M., Kluwer, B., Rohringer, A., & Meijerink, H. (2024). Covid-19 and influenza vaccine effectiveness against associated hospital admission and death among individuals over 65 years in Norway: A population-based cohort study, 3 October 2022 to 20 June 2023. *Vaccine, 42*(3), 620-628. doi:https://dx.doi.org/10.1016/j.vaccine.2023.12.050

Imran, M., Puig-Barbera, J., Ortiz, J., Lopez-Gonzalez, L., Dean, A., Bonafede, M., & Haag, M. D. M. (2024). Relative Effectiveness of the MF59-Adjuvanted Influenza Vaccine Versus High-Dose and Non-Adjuvanted Influenza Vaccines in Preventing Cardiorespiratory Hospitalizations During the 2019-2020 US Influenza Season. *Influenza and other respiratory viruses, 18*(4), e13288. doi:https://dx.doi.org/10.1111/irv.13288

Imran, M., Mills, C. W., McDermott, K. W., Dean, A., Bogdanov, A., McGovern, I., & Haag, M. D. M. (2024). Relative Effectiveness of the MF59-Adjuvanted Influenza Vaccine Versus High-Dose Influenza Vaccine in Older Adults With Influenza Risk Factors During the 2019-2020 US Influenza Season. *Open forum infectious diseases, 11*(8), ofae459. doi:https://dx.doi.org/10.1093/ofid/ofae459

**Non-eligible intervention (n = 1)**

Al Qahtani, A. A., Selim, M., Hamouda, N. H., Al Delamy, A. L., Macadangdang, C., Al Shammari, K. H., & Al Shamary, S. F. (2020). Seasonal influenza vaccine effectiveness among health-care workers in Prince Sultan Military Medical City, Riyadh, KSA, 2018-2019. *Human Vaccines and Immunotherapeutics*, 1-5. doi:https://dx.doi.org/10.1080/21645515.2020.1764827

**Non-eligible comparator (n = 3)**

Kislaya, I., Torres, A. R., Gomes, L., Melo, A., Machado, A., Henriques, C., . . . Rodrigues, A. P. (2023). End of season 2022/2023 quadrivalent influenza vaccine effectiveness in preventing influenza in primary care in Portugal. *Human Vaccines and Immunotherapeutics, 19*(3), 2263219. doi:https://dx.doi.org/10.1080/21645515.2023.2263219

Stuurman, A. L., Carmona, A., Biccler, J., Descamps, A., Levi, M., Baum, U., . . . Diez-Domingo, J. (2023). Brand-specific estimates of influenza vaccine effectiveness for the 2021-2022 season in Europe: results from the DRIVE multi-stakeholder study platform. *Frontiers in public health, 11*, 1195409. doi:https://dx.doi.org/10.3389/fpubh.2023.1195409

Whitaker, H., Willam, N., Cottrell, S., Goudie, R., Andrews, N., Evans, J., . . . Watson, C. (2024). End of 2022/23 Season Influenza Vaccine Effectiveness in Primary Care in Great Britain. *Influenza and other respiratory viruses, 18*(5), e13295. doi:https://dx.doi.org/10.1111/irv.13295

**Unclear study design (n = 1)**

Bricout, H., Levant, M.-C., Assi, N., Crepey, P., Descamps, A., Mari, K., . . . Chit, A. (2024). The relative effectiveness of a high-dose quadrivalent influenza vaccine versus standard-dose quadrivalent influenza vaccines in older adults in France: a retrospective cohort study during the 2021-22 influenza season. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. doi:https://dx.doi.org/10.1016/j.cmi.2024.08.012

**Not enough information (n = 1)**

Biering-Sorensen, T., & Goffin, S. (2023). DANFLU-1: Feasibility of a Pragmatic Randomised Trial to Assess the Relative Effectiveness of High-dose (QIV-HD) vs Standard-dose Quadrivalent Influenza Vaccine (QIV-SD) on Severe Cardio-respiratory Outcomes in Elderly Adults. *Heart Lung and Circulation, 32*(Supplement 3), S352. doi:https://dx.doi.org/10.1016/j.hlc.2023.06.807

## 5. Study characteristics of the vaccine effectiveness and safety studies of the primary review (2020) that met inclusion criteria and the update search (2023)

*Table 1: Key characteristics of vaccine efficacy/effectiveness studies of update*

| Study | Intervention (Comparison) | Study design | Country | Funding | Setting | Outcome | Influenza season | Population | N (vacc) | Mean age in years (SD) | Female sex % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Balasubramani 2020** [4] | **HD-3v** (vs. SD-3/4v) | test-negative | USA | non-industry funded | outpatient | Influenza infection | 2015-16, 2016-17, 2017-18, 2018-19 | ≥ 65 years | 2,993 | HD 73.6 (6.9) SD 73.3 (7.0) | HD 62.3 SD 61.4 |
| **Doyle 2021** [5] | **HD-3v** (vs. SD-3/4v) | test-negative | USA | non-industry funded | inpatient | Influenza-related hospitalisation | 2015-16, 2016-17 | ≥ 65 years | 1,107 | NA | 57.3 |
| **Klein 2020** [6] | **Cell-based-3v** (vs. SD-3/4v) | retro-spective cohort | USA | non-industry funded | outpatient | Influenza infection | 2017-18 | 4-64 years | 1,016,965 | NA | Cell-based 56.9 SD 56.4 |
| **Martin 2021** [7] | **Cell-based-3v** (vs. SD-3/4v) | retro-spective cohort | USA | non-industry funded | inpatient | Influenza-related hospitalisation | 2017-18 | ≥ 18 years | 2,350 | NA | NA |
| **Zimmerman 2023** [8] | **Recombinant- 4v** (vs. SD-3/4v) | test-negative | USA | industry funded | outpatient | medically attended outpatient influenza | 2018-19, 2019-20 | ≥ 18 years, high-risk condition, immuno-compromised | 1,553 | 51.5 (18.8) | 65.6 |
| **Hsiao 2022** [9] | **Recombinant- 4v** (vs. SD-4v) | RCT | USA | industry funded | inpatient | Influenza-related hospitalisation | 2018-19, 2019-20 | ≥ 18-64 years | 1,630,328 | NA | NA |
| **Domnich 2022** [10] | **MF59-3v** (vs. SD-4v) | test-negative | Italy | non-industry funded | inpatient | Influenza-related hospitalisation | 2018-19, 2019-20 | ≥ 65 years | 512 | Cases 78.9 (7.5) Controls 79.6 (7.6) | Cases 50.6 Controls 41.0 |

**HD=** high-dose influenza vaccine; **NA**= not applicable; **SD**= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA); **3v**/**4v**= tri-/quadrivalent

*Table 2: Key characteristic of vaccine efficacy/effectiveness studies of primary review, included in the evidence body of the update review*

| Study | Intervention (Comparison) | Study design | Country | Setting | Outcome | Influenza season | Population | N (vacc) |
|---|---|---|---|---|---|---|---|---|
| **Van Buynder 2013** [11] | **MF59-3v** (vs. SD-3v) | case-control | Canada | Multicentre | Laboratory-confirmed influenza | 2011-2012 | Adults aged ≥ 65 years | 282 |
| **Mira-Iglesias 2019** [12] | **MF59-3v** (vs. SD-3v) | case-control | Spain | Hospital | Laboratory-confirmed influenza | 2017-2018 | Adults aged ≥ 60 years | 1,477 |
| **Pebody 2020a** [13] | **MF59-3v** (vs. SD-3v/4v) | case-control | United Kingdom | General practice and Hospitals | Laboratory-confirmed influenza hospitalization | 2018-2019 | Adults aged ≥ 65 years | 1,439 |
| **Pebody 2020b** [14] | **MF59-3v** (vs. SD-3v/4v) | case-control | United Kingdom | General practice | Laboratory-confirmed influenza | 2018-2019 | Children and adults aged > 0 years | 2,326 |
| **Bellino 2019** [15] | **MF59-3v** (vs. SD-3v/4 | case-control | Italy | General practice | Laboratory-confirmed influenza | 2018-2019 | Children and adults aged ≥ 6 months | 2,526 |
| **Rondy 2017a** [16, 17] | **MF59-3v** (vs. SD-3v) | case-control | Europe | Multicentre, Hospital | Laboratory-confirmed influenza | 2016-2017 | Adults aged ≥ 65 years | 640 |
| **Rondy 2017b** [18] | **MF59-3v** (vs. SD-3v) | case-control | Europe | Multicentre, Hospital | Laboratory-confirmed influenza | 2015-2016 | Adults aged ≥ 65 years | 1,802 |
| **DiazGranados 2014** [19] | **HD-3v** (vs. SD-3v) | RCT | United States and Canada | Multicentre | Laboratory-confirmed ILI | 2011-2013 | Adults aged ≥ 65 years | 31,989 |
| **Bruxvoort 2019** [20] | **Cell-based-3/4** (vs SD-v3/4) | case control | United States | Hospital | Laboratory-confirmed influenza hospitalization | 2017-2018 | Children and Adults (aged ≥ 4 years) | 8,132 |
| **Dunkle 2017a** [21] | **Recombinant- 4v** (vs. SD-4v) | RCT | United States | Multicentre Outpatients | Culture-confirmed influenza-like illness, PCR-confirmed ILI | 2014-2015 | Adults (aged ≥ 50 years) | 9,003 |

**HD=** high-dose influenza vaccine; **NA**= not applicable; **SD**= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA); **3v**/**4v**= tri-/quadrivalent

*Table 3: Key characteristics of vaccine safety studies of update*

| Study | Intervention (Comparison) | Study design | Country | Type of funding | Population | N vaccinated | Mean age in years (SD) | Female sex - % | Safety outcomes available |
|---|---|---|---|---|---|---|---|---|---|
| **Caldera 2020 [22]** | **HD-3v** (vs. SD-4v) | RCT | USA | non-industry funded | Patients with inflammatory bowel disease on anti-tumor necrosis factor alpha agents 18-64 years | 40 | Median (IQR) HD 29 (25to45) SD 43 (32to52) | HD 36 SD 33 | Local and systemic reactions |
| **Chen 2022 [23]** | **HD-4v** (vs. SD-4v) | RCT | Taiwan | industry-funded | ≥ 65 years | 165 | 71.4 (5.52) | HD 57.3 SD 55.4 | Local and systemic reactions SAE |
| **Layton 2020 [24]** | **HD-3v** (vs. SD) | retrospective cohort | USA | not reported | ≥ 65 years with end-stage renal disease | 520,876 | 74.7 (7.0) | 49.5 | Local and systemic reactions SAE |
| **Pepin 2021 [25]** | **HD-4v** (vs. SD-4v) | RCT | Belgium, France, Germany, Italy, Poland, the Netherlands | industry-funded | ≥ 60 years | 1,533 | 66.6 (5.97) | 50.4 | Unsolicited non-serious injection-site AE Unsolicited non-serious systemic AE, SAE, AESI |
| **Sanchez 2023 [26]** | **HD-4v** (vs. SD-4v) | RCT | Japan | industry-funded | > 60 years | 2,100 | HD 68.2 (4.9) SD 68.4 (5.0) | HD 46.3 SD 47.9 | Local and systemic reactions SAE |
| **Pillsbury 2020 [27]** | **HD-3v** (vs. MF59) | retrospective cohort | Australia | non-industry funded | ≥ 65 years | 47,307 | Median (IQR) 71 (68-76) | 54.0 | Local and systemic reactions SAE |
| **Schmader 2021 [28]** | **MF59** (vs. HD) | RCT | USA | non-industry funded | ≥ 65 years | 757 | Median age (range) 72 (65-97) | 55.0 | Local and systemic reactions SAE |
| **de Lusignan 2022 [29]** | **MF59** (vs. SD-4v) | retrospective cohort | UK | non-industry funded | 0-100 years | 1,024,160 | NA | NA | Local and systemic reactions SAE |
| **Hansen 2020 [30]** | **Recombinant-3v** (vs. SD-3v) | retrospective cohort | USA | industry-funded | ≥ 18 years, pregnant women included | 305,659 | NA | Rec 52.7 SD 55.3 | SAE Fever |
| **Hsiao 2022 [31]** | **Recombinant-4v** (vs. SD-4v) | prospective cohort | USA | industry-funded | Chinese adults 18 to 64 years, pregnant women included | 42,684 | 18-65 years | 63.8 | SAEs Fever |

**AE**= adverse event**; AESI**= adverse event**; HD=** high-dose; influenza vaccine; **NA**= not applicable; **SAE**= serious adverse event; **SD**= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA); **3v**/**4v**= tri-/quadrivalent

*Table 4: Key characteristics of vaccine safety studies of primary review, included in the evidence body of the update review*

| Study | Intervention (Comparison) | Study design | Country | Population | N vaccinated | Safety outcomes available |
|---|---|---|---|---|---|---|
| **Cowling 2020** [32] | **MF59-3v** (vs. SD-4v) | RCT | Hong Kong | Community dwelling Adults aged 65–82 years | 1,861 | Local adverse events, Systemic adverse events, Serious adverse events |
| **Cowling 2020** [32] | **Recombinant-3v** (vs. SD-4v) | RCT | Hong Kong | Community dwelling Adults aged 65–82 years | 1,861 | Serious adverse events, Hospitalisation |
| **de Bruijn 2006** [33] | **MF59-3v** (Subunit influenza vaccine) | RCT | Netherlands | Adults aged ≥ 61 years | 386 | Mortality, Serious adverse events, Local adverse events, Systemic adverse events |
| **Durando 2008** [34] | **MF59-3v** (vs. SD-3v) | RCT | Italy | Healthy Adults aged ≥ 65 years | 270 | Serious adverse events, Any adverse event |
| **Frey 2003** [35] | **MF59-3v** (vs. SD-3v) | RCT | United States | Adults aged 18-64 years | 301 | Local adverse events, Systemic adverse events |
| **Frey 2003** [35] | **MF59-3v** (vs. SD-3v) | RCT | United States, Philippines, Panama and Columbia | Adults aged ≥ 65 years | 7,109 | Mortality, Local adverse events Systemic adverse events |
| **Gasparini 2001** [36] | **MF59-3v** (vs. SD-3v) | RCT | Italy | Adults aged 18-65 years, HIV seropositive | 308 | Serious adverse events, Local adverse events, Systemic adverse events |
| **Li 2008** [37] | **MF59-3v** (vs. SD-3v) | RCT | China | Adults aged ≥ 60 years | 600 | Serious adverse events, Local adverse events, Systemic adverse events |
| **Minutello 1999** [38] | **MF59-3v** (vs. SD-3v) | RCT | Italy | Adults aged ≥ 65 years | 92 | Serious adverse events, Local adverse events, Systemic adverse events |
| **Ruf 2004** [39] | **MF59-3v** (vs. SD-3v) | RCT | Germany | Adults aged ≥ 60 years | 827 | Local and general symptoms, Serious adverse events |
| **Scheifele 2013** [40] | **MF59-3v** (vs. SD-3v) | RCT | Canada | Adults aged ≥ 65 years | 922 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Seo 2014** [41] | **MF59-3v** (vs. SD-3v) | RCT | South Korea | Healthy, independently-living adults aged ≥ 65 years | 354 | Local adverse events, Systemic adverse events |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Sindoni 2009** [42] | **MF59-3v** (vs. SD-3v) | RCT | Italy | Adults (aged ≥ 65 years) | 195 | Serious adverse events, Local adverse events, Systemic adverse events |
| **Couch 2007** [43] | **HD-v3** (vs. SD-3v) | RCT | United States | Adults aged ≥ 65 years | 414 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **DiazGranados 2015b** [44] | **HD-v3** (vs. SD-3v) | RCT | United States | Adults aged 50-64 years | 300 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Falsey 2009** [45] | **HD-v3** (vs. SD-3v) | RCT | United States | Adults aged ≥ 65 years | 3,876 | Mortality, Local adverse events, Systemic adverse events |
| **Keitel 2006** [46] | **HD-v3** (vs. SD-3v) | RCT | United States | Adults aged ≥ 65 years | 202 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Tsang 2014** [47] | **HD-v3** (vs. SD-3v) | RCT | United States | Adults aged ≥ 65 years | 1912 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Noh 2019** [48] | **HD-4v** (vs. SD-4v) | RCT | Republic of Korea | Adults aged 19-64 years | 40 | Local adverse events, Systemic adverse events |
| **Pillet 2019** [49] | **HD-4v** (vs. SD-4v) | RCT | United States | Adults aged ≥ 18 years | 750 | Serious adverse events, Local adverse events, Systemic adverse events |
| **Ehrlich 2012** [50] | **Cell-based-3v** (vs. SD-3v) | RCT | United States | Adults aged > 50 years | 3,208 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Frey 2010** [51] | **Cell-based-3v** (vs. SD-3v) | RCT | United States, Poland and France | Healthy adults aged 18-49 years | 11,404 | Serious adverse events, Local adverse events, Systemic adverse events |
| **Groth 2009** [52] | **Cell-based-3v** (vs. SD-3v) | RCT | Germany | Adults aged ≥ 18 years | 240 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Halperin 2002** [53] | **Cell-based-3v** (vs. SD-3v) | RCT | Canada | Adults and children aged ≥ 3 years | 940 | Local adverse events, Systemic adverse events |
| **Song 2015** [54] | **Cell-based-3v** (vs. SD-3v) | RCT | Republic of Korea | Adults aged ≥ 19 years | 1,155 | Serious adverse events, Local adverse events, Systemic adverse events |
| **Szymczakiewicz-Multanowska 2009** [55] | **Cell-based-3v** (vs. SD-3v) | RCT | Poland | Adults aged ≥ 18 years | 2,654 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Dunkle 2017a** [56] | **Recombinant-3v** (vs. SD-4v) | RCT | United States | Adults aged ≥ 50 years | 9,003 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Dunkle 2017b** [21] | **Recombinant-3v** (vs. SD-4v) | RCT | United States | Adults aged 15-49 years | 1,350 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Baxter 2011** [57] | **Recombinant-3v** (vs. SD-3v) | RCT | United States | Healthy adults aged 50-64 years | 602 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Izikson 2015** [58] | **Recombinant-3v** (vs. SD-3v) | RCT | United States | Adults aged ≥ 50 years | 2,640 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Keitel 2009** [59] | **Recombinant-3v** (vs. SD-3v) | RCT | United States | Adults aged ≥ 65 years | 869 | Serious adverse events, Mortality, Local adverse events, Systemic adverse events |
| **Treanor 2006** [60] | **Recombinant-3v** (vs. SD-3v) | RCT | United States | Adults aged ≥ 18 years | 399 | Local adverse events, Systemic adverse events |

**AE**= adverse event**; AESI**= adverse event**; HD=** high-dose; influenza vaccine; **NA**= not applicable; **SAE**= serious adverse event; **SD**= standard influenza vaccine (egg-based standard-dose influenza vaccine containing 15 µg HA); **3v**/**4v**= tri-/quadrivalent

# 6. Risk of bias assessment of studies included in update review

## 6.1. Risk of bias efficacy/effectiveness studies

**Outcome: Laboratory confirmed influenza**

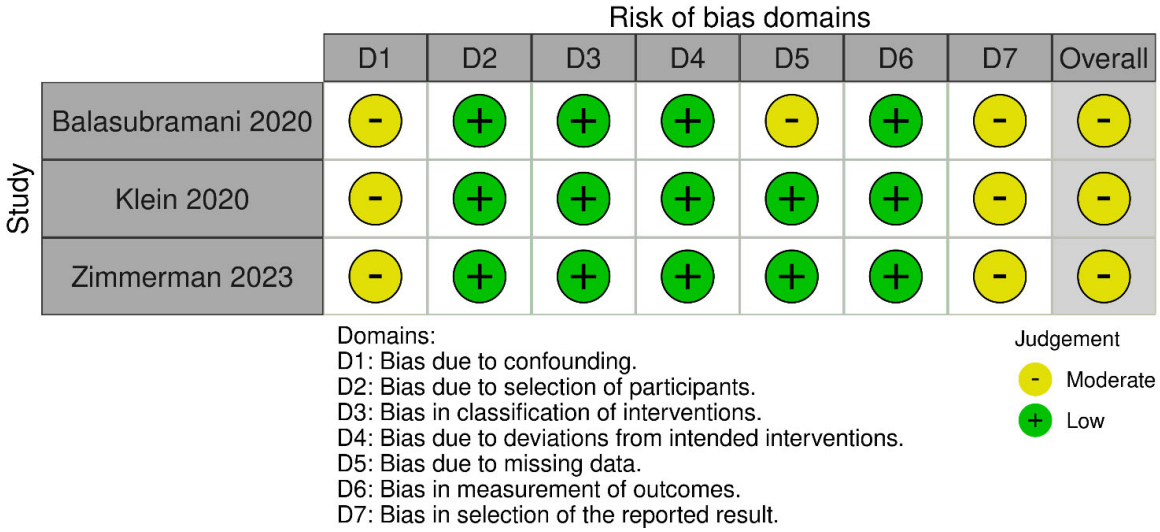


*Figure 3: Risk of bias VE-studies (assessed with ROBINS-I); outcome: laboratory confirmed influenza*

**Outcome: Influenza-associated hospitalisation (Laboratory confirmed)**

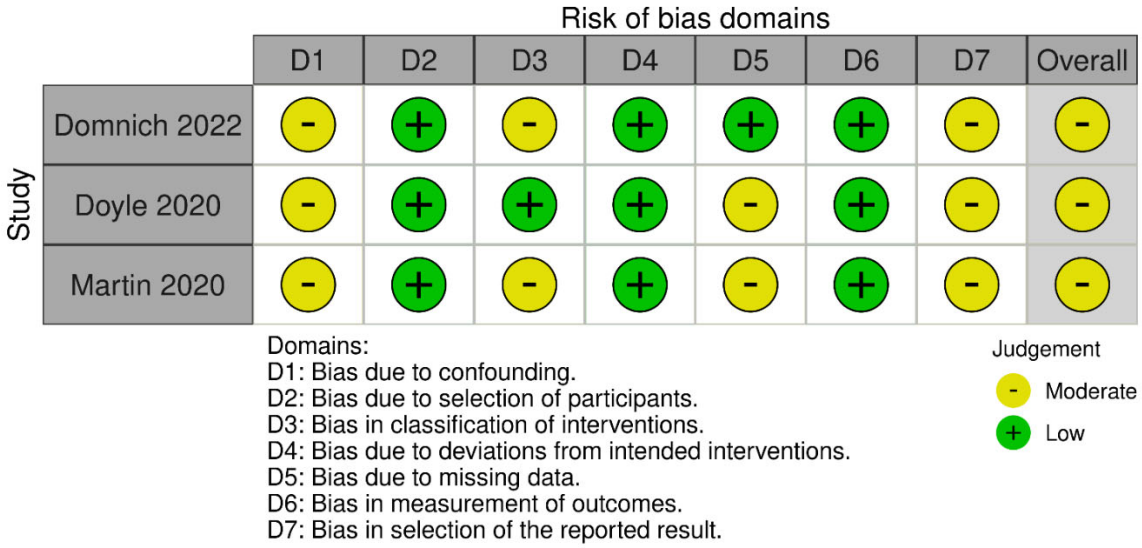


*Figure 4: Risk of bias in VE-studies (assessed with ROBINS-I); outcome: laboratory confirmed hospitalization*

## 6.2. Risk of bias safety studies

***Outcome: Serious adverse events (SAE) – non-randomized studies of intervention (NRSI)***

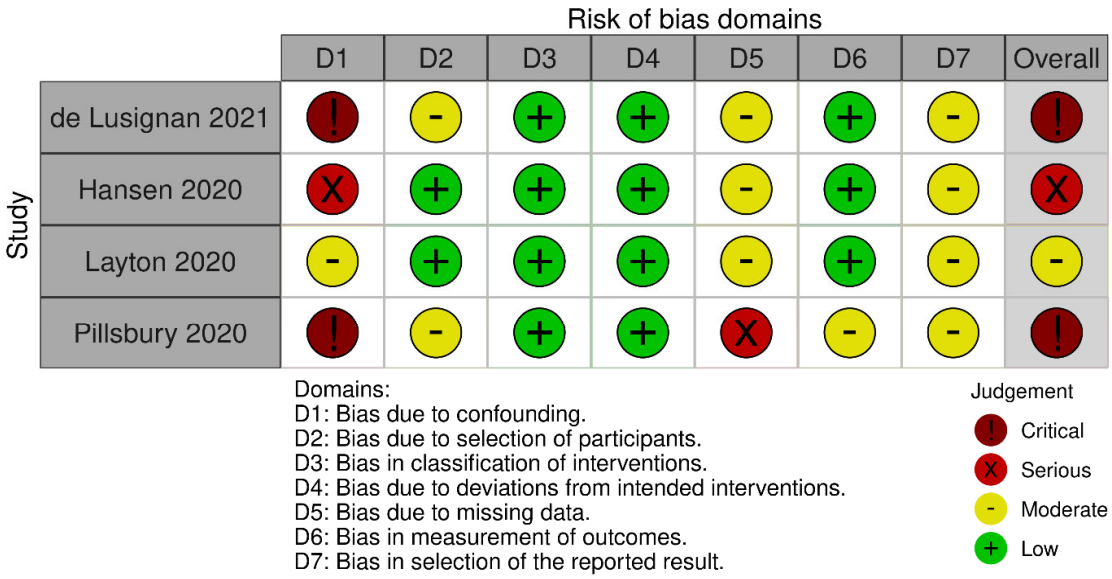


*Figure 5: Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: SAE (serious adverse events)*

**Outcome: Fever - non-randomized studies of intervention (NRSI)**

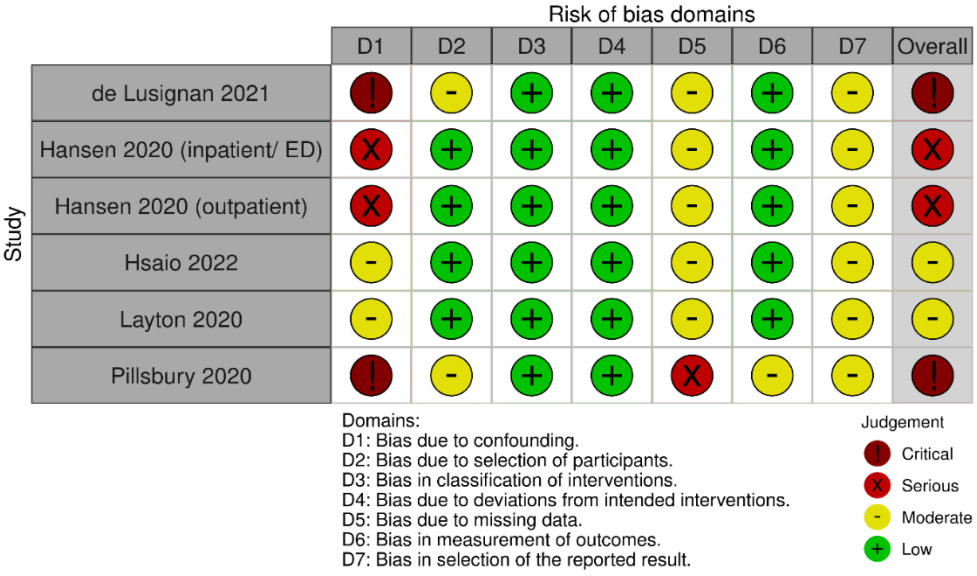


*Figure 6: Risk of bias in NRSI on safety (assessed with ROBINS-I); outcome: Fever*

**Outcome: SAE – randomized controlled trials (RCT)**

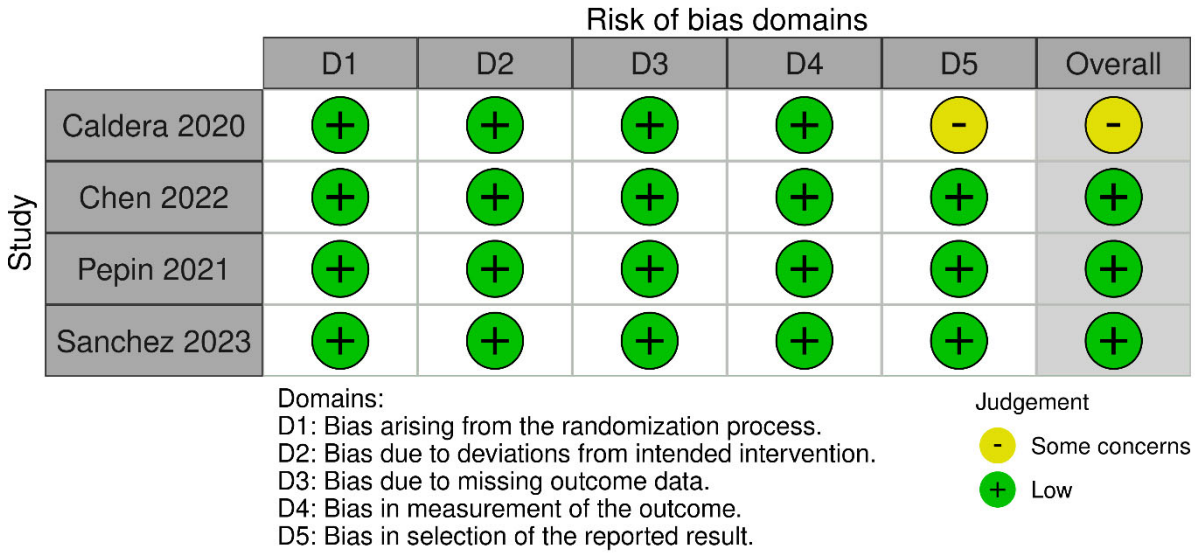


*Figure 7: Risk of bias in RCT safety-studies (assessed with RoB2); outcome: SAE (serious adverse events)*

**Outcome: Fever - RCT**

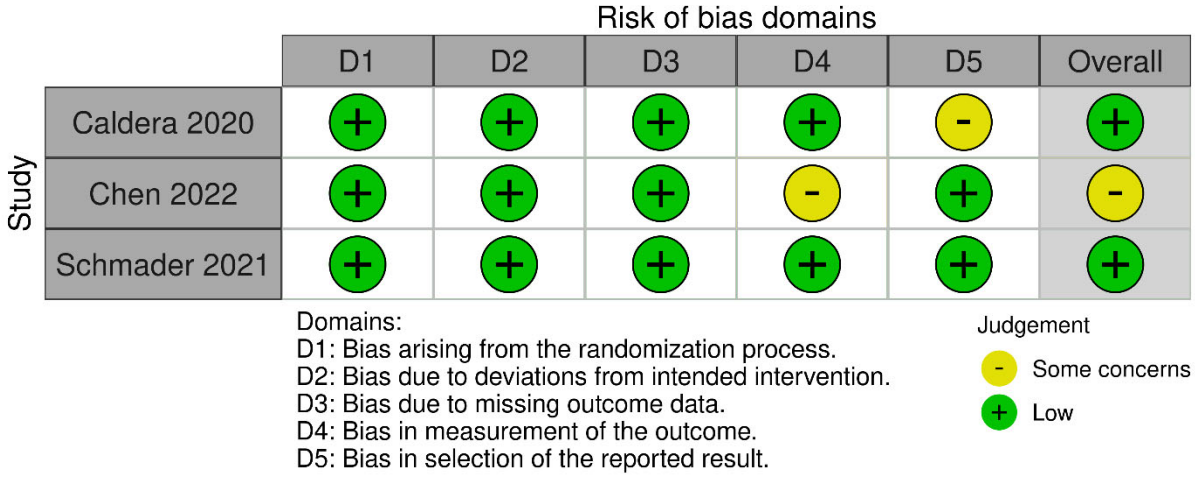


*Figure 8: Risk of bias in RCT safety-studies (assessed with RoB 2); outcome: Fever*

# 7. Effectiveness and safety of the newer and enhanced seasonal influenza vaccines

*Table 5: Summary of findings relative effectiveness and safety of **MF59-adjuvanted influenza vaccine** vs. standard influenza vaccine in adults*

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | With standard influenza vaccine | MF59-adjuvanted influenza vaccine | **Difference** | | |
| Laboratory confirmed influenza<br>№ of participants: 10.492<br>(7 observational studies) | **rVE-range:**<br>**-30**<br>(-146 to 31)<br>**to 88**<br>(51 to 100) | N. A. | N. A. | N.A. | ⨁⨁◯◯<br>Low[a,b] | MF59-adjuvanted influenza vaccines may or may not reduce laboratory-confirmed influenza infection in adults compared to standard vaccine. |
| Influenza related hospitalisation (laboratory confirmed)<br>№ of participants: 512<br>(1 observational study) | **rVE 59.2**<br>(14.6 to 80.5) | N.A. | N.A. | N.A. | ⨁⨁⨁◯<br>Moderate[a] | MF59-adjuvanted influenza vaccines probably reduce hospitalisation related to laboratory-confirmed influenza infection in adults compared to standard vaccine. |
| Influenza-related death (laboratory confirmed) | - | - | - | - | - | no data reported |
| Serious adverse event (SAE)<br>№ of participants: 8356<br>(3 RCTs) | **RR 0.95**<br>(0.19 to 4.72) | 0.1% | **0.1%**<br>(0 to 0.3) | **0.0% fewer**<br>(0.1 fewer to 0.3 more) | ⨁⨁◯◯<br>Low[c,d] | MF59-adjuvanted influenza vaccines may result in little to no difference in serious adverse events (SAEs) compared to the standard vaccine. |
| Idiopathic thrombocytopenic purpura | - | - | - | - | - | no data reported |
| Narcolepsy/cataplexy | - | - | - | - | - | no data reported |
| Guillain–Barré syndrome (GBS) | - | - | - | - | - | no data reported |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations**
a. Residual confounding cannot be excluded
b. Heterogeneous point estimates between the studies.
c. High risk of bias in 2 out of 3 studies.
d. Wide confidence interval.

*Table 6: Summary of findings relative effectiveness and safety of **high-dose influenza vaccine** vs. standard influenza vaccine in adults*

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | With standard influenza vaccine | High-dose influenza vaccine | Difference | | |
| Laboratory confirmed influenza (lab confirmed)<br>assessed with: PCR<br>№ of participants: 31989<br>(1 RCT) | **rVE 24**<br>**(11 to 36)** | 1.9% | **1.4**%<br>(1.2 to 1.7) | **0.5**% **fewer**<br>(0.7 fewer to 0.2 fewer) | ⊕⊕⊕◯<br>Moderate[a] | High-dose influenza vaccines probably slightly reduce laboratory-confirmed influenza infection in adults. |
| Influenza related hospitalisation (laboratory confirmed)<br>assessed with: PCR<br>№ of participants: 1107 (1 NRSI) | **rVE 27**<br>(-1 to 48) | N.A. | N.A. | N.A. | ⊕⊕◯◯<br>Low[b,c] | High-dose influenza vaccines may slightly reduce hospitalisation related to laboratory-confirmed influenza infection in adults. |
| Influenza-related death (laboratory confirmed) | - | - | - | - | - | no data reported |
| Serious adverse events (SAE)<br>№ of participants: 9034<br>(6 RCTs) | **RR 1.02**<br>(0.42 to 2.46) | 0.2% | **0.2**%<br>(0.1 to 0.6) | **0.0**% **fewer**<br>(0.1 fewer to 0.4 more) | ⊕⊕◯◯<br>Low[c,d] | High-dose influenza vaccines may result in little to no difference in serious adverse events (SAEs) related to vaccination. |
| Idiopathic thrombocytopenic purpura | - | - | - | - | - | no data reported |
| Narcolepsy/cataplexy | - | - | - | - | - | no data reported |
| Guillain–Barré syndrome (GBS) | - | - | - | - | - | no data reported |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations**
a. One RCT with moderate risk of bias.
b. Residual confounding can not be excluded.
c. Wide confidence interval.
d. 3 out of 6 studies moderate risk of bias.

*Table 7: Summary of findings relative effectiveness and safety of **cell-based influenza vaccine** vs. standard influenza vaccine in adults*

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | With standard influenza vaccine | With cell-based influenza vaccine | **Difference** | | |
| Laboratory confirmed influenza (lab confirmed)<br>assessed with: PCR<br>№ of participants: 1,025,097<br>(2 observational studies) | **rVE-range**<br>**-5.8**<br>(-36.1 to 17.7)<br>**to 21.4**<br>(-7.3 to 42.4) | N.A. | N.A. | N.A. | ⊕⊕◯◯<br>Low[a] | Cell-based influenza vaccines may or may not reduce laboratory-confirmed influenza infection in adults. |
| Influenza related hospitalisation (laboratory confirmed)<br>assessed with: PCR<br>№ of participants: 1741<br>(1 observational study) | **rVE 8.5**<br>(-75.9 to 52.3) | N.A. | N.A. | N.A. | ⊕⊕◯◯<br>Low[a,b] | Evidence is uncertain, whether cell-based influenza vaccines reduce hospitalisation related to laboratory-confirmed influenza infection in adults. |
| Influenza-related death (laboratory confirmed) | - | - | - | - | - | no data reported |
| Serious adverse events (SAE)<br>№ of participants: 3208<br>(1 RCT) | **RR 0.39**<br>(0.02 to 9.49) | N.A. | N.A. | N.A. | ⊕⊕◯◯<br>Low[b] | Cell-based influenza vaccines may or may not decrease serious adverse events (SAEs) related to vaccination. |
| Idiopathic thrombocytopenic purpura | - | - | - | - | - | no data reported |
| Narcolepsy/cataplexy | - | - | - | - | - | no data reported |
| Guillain–Barré syndrome (GBS) | - | - | - | - | - | no data reported |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations**
a. Residual confounding can not be excluded.
b. Wide confidence interval.

*Table 8: Summary of findings relative effectiveness and safety of **recombinant influenza vaccine** vs. standard influenza vaccine in adults*

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | With standard influenza vaccine | With recombinant influenza vaccine | Difference | | |
| Laboratory confirmed influenza (lab confirmed)<br>assessed with: PCR<br>№ of participants: 8855<br>(1 RCT) | **rVE 30**<br>(10 to 47) | **3.1%** | **2.2%**<br>(1.7 to 2.8) | **0.9% fewer**<br>(1.5 fewer to 0.3 fewer) | ⊕⊕⊕◯<br>Moderate[a] | Recombinant influenza vaccines probably slightly reduce laboratory-confirmed influenza infection in adults. |
| Influenza related hospitalisation (laboratory confirmed)<br>assessed with: PCR<br>№ of participants: 1,630,328<br>(1 RCT) | - | Certainty of the evidence could not be assessed due to lack of information. | | - | - | N.A. |
| Influenza-related death (laboratory confirmed) | - | - | - | - | - | no data reported |
| Serious adverse events (SAE)<br>№ of participants: 907<br>(2 RCTs) | **RR 3.04**<br>(0.32 to 29.10) | N.A. | N.A. | N.A. | ⊕⊕◯◯<br>Low[b] | Recombinant influenza vaccines may or may not result in an increase in serious adverse events (SAEs) related to vaccination. |
| Idiopathic thrombocytopenic purpura<br>№ of participants: 42.684<br>(1 observational study) | **OR 0.52**<br>(0.15 to 1.50) | N.A. | N.A. | N.A. | ⊕⊕◯◯<br>Low[c,d] | Recombinant influenza vaccines may or may not result in an decrease in of idiopathic thrombocytopenic purpura related to vaccination. |
| Narcolepsy/cataplexy<br>№ of participants: 305.659<br>(1 observational study) | **OR 0**<br>(0 to 6) | N.A. | N.A. | N.A. | ⊕◯◯◯<br>Very low[d,e] | Evidence is uncertain about the effect of recombinant influenza vaccines on narcolepsy/cataplexy related to vaccination. |
| Guillain–Barré syndrome (GBS)<br>№ of participants: 305.659<br>(1 observational study) | **OR 0.00**<br>(0.00 to 16.07) | N.A. | N.A. | N.A. | ⊕◯◯◯<br>Very low[d,e] | Evidence is uncertain about the effect of recombinant influenza vaccine on Guillain–Barré syndrome related to vaccination. |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio; **rVE**: relative vaccine effectiveness [(1 – Risk Ratio) *100%]

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

## 8. GRADE profile for certainty of evidence for important and critical outcomes and summery of findings table of the update systematic review with data as of July 2023

### 8.1. GRADE profile for the MF-59 adjuvanted influenza vaccine

**MF-59 adjuvanted influenza vaccine compared to standard influenza vaccine for people ≥ 18 years old**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard influenza vaccine | With MF-59 adjuvanted influenza vaccine | Relative effect (95% CI) | Risk with standard influenza vaccine | Risk difference with MF-59 adjuvanted influenza vaccine |
| **Laboratory confirmed influenza (assessed with: PCR)** | | | | | | | | | | | |
| participants: 10.492 (7 non-randomised studies) | serious[a] | serious[b] | not serious | not serious | none | ⨁⨁◯◯ Low | **rVE-range**: -30 (-146 to 31) to 88 (51 to 100) | | | | |
| **Laboratory confirmed hospitalisation (assessed with: PCR)** | | | | | | | | | | | |
| Nº of participants: 512 (1 non-randomised study) | serious[a] | not serious | not serious | not serious | none | ⨁⨁⨁◯ Moderate | - | | **rVE 59.2** (14.6 to 80.5) | **low** | |
| | | | | | | | | | | 0 per 100,000 | **-- per 100,000** (from -- to --) |
| **Serious adverse event** | | | | | | | | | | | |
| Nº of participants: 8356 (3 RCTs) | serious[c] | not serious | not serious | serious[d] | none | ⨁⨁◯◯ Low | 3/4080 (0.1%) | 3/4276 (0.1%) | **RR 0.95** (0.19 to 4.72) | 3/4080 (0.1%) | **4 fewer per 100,000** (from 60 fewer to 274 more) |
| **Laboratory confirmed death - not reported** | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - |

**CI:** confidence interval; **RR:** risk ratio

## Explanations

**a.** Residual confounding cannot be excluded; **b.** Heterogeneous point estimates between the studies; **c.** High risk of bias in 2 out of 3 studies; **d.** Wide confidence interval.

### 8.2. GRADE profile for the high-dose influenza vaccine

**High-dose influenza vaccine compared to standard vaccination for ≥ 18 years old**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard vaccination | With High-dose influenza vaccine | Relative effect (95% CI) | Risk with standard vaccination | Risk difference with High-dose influenza vaccine |
| **Laboratory confirmed influenza (assessed with: PCR)** | | | | | | | | | | | |
| № of participants: 31989 (1 RCT) | serious[a] | not serious | not serious | not serious | none | ⨁⨁⨁◯ Moderate | 301/15998 (1.9%) | 228/15991 (1.4%) | **RR 0.76** (0.64 to 0.90) | 301/15998 (1.9%) | **5 fewer per 1,000** (from 7 fewer to 2 fewer) |
| **Laboratory confirmed hospitalisation (assessed with: PCR)** | | | | | | | | | | | |
| № of participants: 1107 (1 non-randomised study) | serious[b] | not serious | not serious | serious[c] | none | ⨁⨁◯◯ Low | - | | **rVE 27** (-1 to 48) | **Low** | |
| | | | | | | | | | | 0 per 1,000 | **-- per 1,000** (from -- to --) |
| **Serious adverse events** | | | | | | | | | | | |
| № of participants: 9034 (6 RCTs) | serious[d] | not serious | not serious | serious[c] | none | ⨁⨁◯◯ Low | 9/3730 (0.2%) | 12/5304 (0.2%) | **RR 1.02** (0.42 to 2.46) | 9/3730 (0.2%) | **0 fewer per 1,000** (from 1 fewer to 4 more) |
| **Laboratory confirmed death - not reported** | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - |

**CI:** confidence interval; **RR:** risk ratio

## Explanations:

**a.** One RCT with moderate risk of bias; **b.** Residual confounding cannot be excluded; **c.** Wide confidence interval; **d.** 3 out of 6 studies moderate risk of bias.

### 8.3. GRADE profile for the cell-based influenza vaccine

**Cell-based influenza vaccine compared to standard vaccine for > 18 years old**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard vaccine | With cell-based influenza vaccine | Relative effect (95% CI) | Risk with standard vaccine | Risk difference with cell-based influenza vaccine |
| **Laboratory confirmed influenza (assessed with: PCR)** | | | | | | | | | | | |
| Number of participants: 1,025,097 2 non-randomised studies | serious[a] | serious | not serious | not serious | none | ⨁⨁◯◯ Low | rVE-range: -5.8% to 21.4% | | | | |
| **Laboratory confirmed hospitalisation (assessed with: PCR)** | | | | | | | | | | | |
| Number of participants: 1741 (1 non-randomised study) | serious[a] | not serious | not serious | serious[b] | none | ⨁⨁◯◯ Low | | | **rVE 8.5** (-75.9 to 52.3) | | **-- per 1,000** (from -- to --) |
| **Serious adverse events** | | | | | | | | | | | |
| 3208 (1 RCT) | serious | not serious | not serious | serious[b] | none | ⨁⨁◯◯ Low | 0/366 (0.0%) | 1/2842 (0.0%) | **RR 0.39** (0.02 to 9.49) | 0/366 (0.0%) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) |
| **Laboratory confirmed death - not reported** | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - |

**CI:** confidence interval; **RR:** risk ratio

## Explanations

**a.** Residual confounding cannot be excluded; **b**. Wide confidence interval.

### 8.4. GRADE profile for the recombinant influenza vaccine

**Recombinant influenza vaccine compared to standard influenza for ≥ 18 years old**

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard influenza | With recombinant influenza vaccine | Relative effect (95% CI) | Risk with standard influenza | Risk difference with recombinant influenza vaccine |
| **Laboratory confirmed influenza (assessed with: PCR)** | | | | | | | | | | | |
| Number of participants: 8855 (1 RCT) | serious[a] | not serious | not serious | not serious | none | ⨁⨁⨁◯ Moderate | 138/4428 (3.1%) | 96/4427 (2.2%) | **RR 0.70** (0.53 to 0.90) | 138/4428 (3.1%) | **9 fewer per 1,000** (from 15 fewer to 3 fewer) |
| **Laboratory confirmed hospitalisation (assessed with: PCR)** | | | | | | | | | | | |
| Number of participants: 1,630,328 (1 RCT) | | | | | | - | Certainty of the evidence could not be assessed due to lack of data. | | | | |
| **Serious adverse events** | | | | | | | | | | | |
| Number of participants: 907 (2 RCTs) | serious[b] | not serious | not serious | serious | none | ⨁⨁◯◯ Low | 0/456 (0.0%) | 2/451 (0.4%) | **RR 3.04** (0.32 to 29.10) | 0/456 (0.0%) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) |
| **Laboratory confirmed death - not reported** | | | | | | | | | | | |
| - | - | - | - | - | - | - | - | - | - | - | - |

**Idiopathic thrombocytopenic purpur**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of participants: 42 684 (1 non-randomised study) | serious[c] | not serious | not serious | serious[d] | none | ⊕⊕◯◯ Low | | | **OR 0.52** (0.15 to 1.50) | | **1 fewer per 1,000** (from 2 fewer to 0 fewer) |

**Narcolepsy/cataplexy**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of participants: 305 659 (1 non-randomised study) | very serious[e] | not serious | not serious | serious[d] | none | ⊕◯◯◯ Very low | | | **OR 0** (0 to 6) | | **-- per 1,000** (from 6 fewer to --) |

**Guillain–Barré syndrome**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of participants: 305 659 1 non-randomised study | very serious[e] | not serious | not serious | serious[d] | none | ⊕◯◯◯ Very low | | | **OR 0.00** (0.00 to 16.07) | | **-- per 1,000** (from 16 fewer to --) |

**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

## Explanations

**a.** One RCT with moderate risk of bias; **b.** Two RCTs with moderate risk of bias; **c.** Residual confounding cannot be excluded; **d.** Wide confidence interval; **e.** No adjustment for co-morbidities, even though there was a significant difference between the groups.

# 9. Evidence-to-Decision-Tabellen (EtD) für die Empfehlung der STIKO zur Anwendung von Hochdosis oder MF-59 adjuvantierten Influenza-Impfstoffen für Personen ≥ 60 Jahre

## 9.1. EtD-Tabelle für die Standardimpfempfehlung der STIKO zur Anwendung von Hochdosis oder MF-59 adjuvantierten Influenza-Impfstoffen

| **Fragestellung**<br>**Sollen hochdosierte oder MF-59 adjuvantierte Influenza-Impfstoffe gleichwertig bei Personen ≥ 60 Jahre eingesetzt werden?** | | |
|---|---|---|
| **POPULATION:** | Personen ≥ 60 Jahre | |
| **INTERVENTION:** | Impfung mit einem hochdosierten oder MF-59 adjuvantierten Influenza-Impfstoff (trivalent oder quadrivalent) | |
| **VERGLEICH:** | Impfung mit einem konventionellen Influenza-Impfstoff oder mit einem hochdosierten oder MF-59 adjuvantierten Influenza-Impfstoff (trivalent oder quadrivalent) (head-to-head Vergleich) | |
| **ENDPUNKTE:** | **Effektivität:**<br>• Laborbestätigte Influenza<br>• Influenza-bedingte Mortalität (laborbestätigt)<br>• Influenza-bedingte Hospitalisierung (laborbestätigt)<br>• Influenza-assoziierte kardiovaskuläre Erkrankung (laborbestätigt)<br>• Influenza-assoziierte Pneumonie oder untere Atemwegserkrankung (laborbestätigt)<br>• Influenza-like illness (gemäß international akzeptierter Definition, z. B. nach WHO, US CDC, EU) | **Sicherheit:**<br>• Schwerwiegende unerwünschte Ereignisse (SAE)<br>• Reaktogenität lokal und systemisch, jeglicher Schwere |
| **IMPFZIEL:** | Ziel der Impfempfehlung ist die Reduktion schwerer Influenza-assoziierter Atemwegserkrankungen sowie der daraus resultierenden Folgen wie Hospitalisierung, intensivmedizinische Behandlung und Tod bei Personen ≥ 60 Jahre in Deutschland. | |

**Public-Health-Relevanz von Influenza-Erkrankungen bei Personen ≥ 60 Jahren**

**EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN**

- Influenza ist nach COVID-19 eine der häufigsten impfpräventablen Infektionskrankheiten in Deutschland
- Saison 2023/2024: **Influenza-Meldefälle** bei Personen ≥ 60 Jahre: **62.451** (Saison 2022/23: ca. 56.400); dies entspricht für diese Altersgruppe einer Inzidenz von **281 Meldefällen/100.000** Personen (Saison 2022/23: 254/100.000)
- **Hospitalisierungen** im Jahr 2023 (Daten des Instituts für das Entgeltsystem im Krankenhaus [InEK]): **10.290** (2022: 14.588) bei Personen ≥ 60 Jahre aufgrund einer Infektion mit Influenzaviren (ICD10-Hauptdiagnosecode J10). Dies entspricht einer Inzidenz von **41** Hospitalisierungen aufgrund einer Influenza-Infektion **pro 100.000 Personen** bei ≥ 60-Jährigen (2022: 61/100.000).
- **Todesfälle**: Von den 10.290 hospitalisierten Personen sind **852** (2022: 1.270) Personen aufgrund einer Influenza-Erkrankung verstorben.
- Die tatsächliche Anzahl von Influenza-Fällen, Hospitalisierungen und Todesfällen unterliegt einer erheblichen Untererfassung

**GESAMTEINSCHÄTZUNG DER STIKO: Die Verhinderung von Influenza-Erkrankungen bei Personen ≥ 60 Jahre hat aufgrund ihrer relevanten Krankheitslast, der schweren Symptomatik, dem hohen Anteil notwendiger stationärer Behandlungen und beobachteter Todesfälle eine deutliche Public-Health-Relevanz.**

## Erwünschter Effekte (Nutzen/Benefits)

### EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN

- Zusammenfassung der Effektivität von Hochdosis- bzw. MF-59 adjuvantierten Influenza-Impfstoffen in Vergleich zum Standardimpfstoff oder im Vergleich zueinander (head-to head)

| Effektivität von Hochdosis- bzw. MF-59 adjuvantierten Influenza-Impfstoffen im Vergleich zum Standardimpfstoff | |
|---|---|
| **Lab-confirmed influenza** | **Lab-confirmed hospitalisation** |
| ▪ **MF-59 adjuvanted vaccine:**<br>▪ 7 NRSI: **variable rVE [**-30 (-146 to 31) to 88 (51 to 100)] (2020 review) | ▪ **MF-59 adjuvanted vaccine:**<br>▪ 1 NRSI: **rVE 59%** [15 to 81] (2024 SR update) |
| ▪ **High-dose (HD) vaccine:**<br>▪ 1 RCT: **rVE 24.4%** [10 to 37] (2020 review)<br>▪ Not confirmed by 1 NRCT (**rVE: 10%** [-15 to 30]) (2024 SR update) | ▪ **High-dose (HD) vaccine:**<br>▪ 1 NRSI: **rVE 27%** [-1 to 48] (2024 SR update) |

| Effektivität des Hochdosis- bzw. MF-59 adjuvantierten Influenza-Impfstoffs im head-to-head Vergleich | |
|---|---|
| | **Lab-confirmed hospitalisation** |
| | ▪ **MF-59 adjuvanted vaccine vs. High-dose (HD) vaccine:**<br>▪ 1 NRSI: rVE **–2.5%** [-20 to 12] (McGovern 2024) |

| | |
|---|---|
| **EINSCHÄTZUNG DER STIKO HD oder MF-59 Adj. vs. SD: Hochdosis und MF-59 adjuvantierte Influenza-Impfstoffe zeigen eine verbesserte Effektivität bei der Verhinderung von Influenza-Erkrankungen im Vergleich zu den Standardimpfstoffen. Die klinische Wirksamkeit und damit der Nutzen der Impfung im Vergleich zu SD-Impfstoff wird von der STIKO für Personen ≥ 60 Jahre *als mäßig (moderate)* eingeschätzt.** | **EINSCHÄTZUNG DER STIKO HD vs. MF-59 Adj.: Im Vergleich zueinander sind die beiden Impfstoffe bei ihrer Effektivität als gleichwertig zu betrachten. Die Unterschiede in der klinischen Wirksamkeit und damit der Unterschied im Nutzen der Impfung zwischen beiden Impfstoffen wird von der STIKO für Personen ≥ 60 Jahre als *gering (small)* eingeschätzt.** |

## Unerwünschte Effekte (Schaden/Harms)

### EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN

- Zusammenfassung der Sicherheitsendpunkte zu Hochdosis- bzw. MF-59 adjuvantierten Influenza-Impfstoffen in Vergleich zum Standardimpfstoff oder im Vergleich zueinander (head-to head)

| Sicherheit von Hochdosis- bzw. MF-59 adjuvantierten Influenza-Impfstoffen im Vergleich zum Standardimpfstoff | | |
|---|---|---|
| | **MF-59 adjuvanted vaccine vs. SD** | **High-dose (HD) vaccine vs. SD** |
| **SAE** | no group differences (2020 review)<br>no new data in update<br>→ 3 RCT, 2 NRSI | no group differences (2020)<br>no new data in update<br>→ 6 RCT, 3 NRSI |
| **Systemic reaction** | **Fever:**<br>RR: 1.97 (2020)<br>no new data in update (2024)<br>→ 10 RCT | **Headache:**<br>RR: 1.4 (2020)<br>RR: 1.0-2.3 in update (2024)<br>→ 3 RCT |
| **Systemic reaction** | **Pain:**<br>RR 2.02 (2020)<br>no new data in update (2024)<br>→ 12 RCT | **Pain:**<br>RR: 1.5 (2020)<br>RR: 1.1 to 2.2 in update (2024)<br>→ 4 RCT, 1 NRSI |
| **Sicherheit von MF-59 adjuvantierten oder Hochdosis Influenza-Impfstoffen im Vergleich zueinander (head-to-head)** | | |
| **SAE** | No data in 2020 review<br>MF-59 vs. HD in Update 2024:<br>▪ RR: 3.01 (95% CI: 0.82 to 11.02), no vaccine related SAE in either group<br>→ 1 RCT | |
| **Systemic reaction** | No data in 2020 review<br>MF-59 vs. HD in Update 2024:<br>▪ **Headache,** RR: 1.10 [95% CI: 0.73 to 1.66]<br>▪ **Fever (any**), RR: 0.80 [95% CI: 0.38 to 1.68]<br>→ 1 RCT | |
| **Systemic reaction** | No data in 2020 review<br>MF-59 vs. HD in Update 2024:<br>▪ **Pain, RR**: 0.85 [95% CI: 0.66 to 1.10]<br>→ 1 RCT | |

- HD und MF-59 adjuvantierte Influenza-Impfstoffen zeigen im Vergleich zum Standardimpfstoff eine leicht erhöhte Rate an zeitlich begrenzten lokalen und systemischen Reaktionen. In Vergleich zueinander unterscheiden sich HD oder MF-59 adjuvantierte Impfstoffe kaum.
- Es gibt kein Risiko für eine höhere Zahl an SAEs nach Impfung mit HD oder MF-59 adjuvantierten Impfstoffen im Vergleich zum Standardimpfstoff.
- Im Vergleich zueinander zeigt sich numerisch ein erhöhtes relatives Risiko nach Impfung mit dem MF-59 adjuvantierten Impfstoff im Vergleich zum HD Influenza-Impfstoff. Der Wert ist nicht signifikant. Es wurden keine kausal mit dem jeweiligen Impfstoff in Verbindung stehen SAE berichtet.

| | |
|---|---|
| **EINSCHÄTZUNG DER STIKO HD oder MF-59 Adj. vs. SD: Die STIKO schätzt das relative Risiko von unerwünschten Ereignissen nach Impfung mit einem MF-59 adjuvantierten oder HD-Impfstoff im Vergleich zum Standartimpfstoff als *gering (small)* ein.** | **EINSCHÄTZUNG DER STIKO HD vs. MF-59 Adj.: Die STIKO schätzt das relative Risiko von unerwünschten Ereignissen nach Impfung mit einem MF-59 adjuvantierten oder HD-Impfstoff im Vergleich zueinander als *sehr gering (trivial)* ein.** |

## Bewertung der Evidenz nach GRADE und erwartbare absolute Effekte (wenn zu berechnen) für den MF-59 adjuvantierten oder Hochdosis-Impfstoff jeweils im Vergleich zum Standardimpfstoff.

### MF-59 adjuvanted influenza vaccine compared to standard influenza vaccine for people ≥ 18 years old

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard influenza vaccine | With MF-59 adjuvanted influenza vaccine | Relative effect (95% CI) | Risk with standard influenza vaccine | Risk difference with MF-59 adjuvanted influenza vaccine |
| **Laboratory confirmed influenza (assessed with: PCR)** | | | | | | | | | | | |
| Nº of participants: 10.492 (7 non-randomised studies) | serious[a] | serious[b] | not serious | not serious | none | ⨁⨁◯◯ Low | **rVE-range**: -30 (-146 to 31) to 88 (51 to 100) | | | | |
| **Laboratory confirmed hospitalisation (assessed with: PCR)** | | | | | | | | | | | |
| Nº of participants: 512 (1 non-randomised study) | serious[a] | not serious | not serious | not serious | none | ⨁⨁⨁◯ Moderate | - | | **rVE 59.2** (14.6 to 80.5) | **low** | |
| | | | | | | | | | | 0 per 100,000 | **-- per 100,000** (from -- to --) |
| **Serious adverse event** | | | | | | | | | | | |
| Nº of participants: 8356 (3 RCTs) | serious[c] | not serious | not serious | serious[d] | none | ⨁⨁◯◯ Low | 3/4080 (0.1%) | 3/4276 (0.1%) | **RR 0.95** (0.19 to 4.72) | 3/4080 (0.1%) | **4 fewer per 100,000** (from 60 fewer to 274 more) |

### Laboratory confirmed death - not reported

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| - | - | - | - | - | - | - | - | - | - | - | - |

**CI:** confidence interval; **RR:** risk ratio

## Explanations

**a.** Residual confounding cannot be excluded; **b.** Heterogeneous point estimates between the studies; **c.** High risk of bias in 2 out of 3 studies; **d.** Wide confidence interval.

### High-dose influenza vaccine compared to standard vaccination for ≥ 18 years old

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With standard vaccination | With High-dose influenza vaccine | Relative effect (95% CI) | Risk with standard vaccination | Risk difference with High-dose influenza vaccine |
| **Laboratory confirmed influenza (assessed with: PCR)** | | | | | | | | | | | |
| № of participants: 31989 (1 RCT) | serious[a] | not serious | not serious | not serious | none | ⨁⨁⨁◯ Moderate | 301/15998 (1.9%) | 228/15991 (1.4%) | **RR 0.76** (0.64 to 0.90) | 301/15998 (1.9%) | **5 fewer per 1,000** (from 7 fewer to 2 fewer) |
| **Laboratory confirmed hospitalisation (assessed with: PCR)** | | | | | | | | | | | |
| № of participants: 1107 (1 non-randomised study) | serious[b] | not serious | not serious | serious[c] | none | ⨁⨁◯◯ Low | - | | **rVE 27** (-1 to 48) | **Low** | |
| | | | | | | | | | | 0 per 1,000 | **-- per 1,000** (from -- to --) |
| **Serious adverse events** | | | | | | | | | | | |
| № of participants: 9034 (6 RCTs) | serious[d] | not serious | not serious | serious[c] | none | ⨁⨁◯◯ Low | 9/3730 (0.2%) | 12/5304 (0.2%) | **RR 1.02** (0.42 to 2.46) | 9/3730 (0.2%) | **0 fewer per 1,000** (from 1 fewer to 4 more) |

### Laboratory confirmed death - not reported

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| - | - | - | - | - | - | - | - | - | - | - | - |

**CI:** confidence interval; **RR:** risk ratio

## Explanations

**a.** One RCT with moderate risk of bias; **b.** Residual confounding cannot be excluded; **c.** Wide confidence interval; **d.** 3 out of 6 studies moderate risk of bias.

**Bewertung der Evidenz nach GRADE und erwartbare absolute Effekte (wenn zu berechnen) für den MF-59 adjuvantierten versus den Hochdosis-Impfstoff (head to head).**

### MF-59 adjuvanted influenza vaccine compared to high dose influenza vaccine for people 60 years and older

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Study event rates (%) | | | Anticipated absolute effects | |
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | With high dose influenza vaccine | With MF-59 adjuvanted influenza vaccine | Relative effect (95% CI) | Risk with high dose influenza vaccine | Risk difference with MF-59 adjuvanted influenza vaccine |
| **Laboratory-confirmed influenza** | | | | | | | | | | | |
| 24152 (1 non-randomised study) | serious[a] | not serious | not serious | serious[b] | none | ⨁⨁◯◯ Low[a,b] | 4327/22042 (19.6%) | 374/2110 (17.7%) | **OR 1.025** (0.878 to 1.196) | 4327/22042 (19.6%) | **4 more per 1,000** (from 20 fewer to 30 more) |
| **Influenza-related hospitalization (lab-confirmed)** | | | | | | | | | | | |
| 22102 (1 non-randomised study) | serious[a] | not serious | not serious | serious[b] | none | ⨁⨁◯◯ Low[a,b] | 2890/20113 (14.4%) | 286/1989 (14.4%) | **OR 1.016** (0.843 to 1.225) | 2890/20113 (14.4%) | **2 more per 1,000** (from 20 fewer to 27 more)[c] |

**serious adverse events**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 757 (1 RCT) | not serious | not serious | not serious | very serious[d] | none | ⨁⨁◯◯ Low[d] | 3/379 (0.8%) | 9/378 (2.4%) | **RR 3.01** (0.82 to 11.02) | 3/379 (0.8%) | **16 more per 1,000** (from 1 fewer to 79 more) |

**Laboratory confirmed death - not reported**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| - | - | - | - | - | - | - | - | - | - | - | - |

**CI:** confidence interval; **OR:** odds ratio; **RR:** risk ratio

## Explanations

**a.** residual confounding cannot be excluded **b.** uncertainty due to wide confidence intervals and low number of studies **c.** with the approximation that 9% of HD or MF-59 vaccinated influenza positive tested persons are vaccinated with MF-59 **d.** uncertainty due to wide confidence intervals and not enough participants to detect rare SAE

| | |
|---|---|
| **EINSCHÄTZUNG DER STIKO zu HD oder MF-59 Adj. vs. SD:**<br>**Die verfügbaren Daten zur relativen Wirksamkeit zu HD und MF-59 adjuvantierten Influenza-Impfstoffen im Vergleich zu Standardimpfstoffen beziehen sich überwiegend auf nicht randomisierte Beobachtungsstudien. Daten zur Sicherheit liegen mehrheitlich aus RCTs vor. Die Vertrauenswürdigkeit der Evidenz zur Wirksamkeit und Sicherheit wird von der STIKO als *moderat (moderate) bis niedrig (low)* eingeschätzt.** | **EINSCHÄTZUNG DER STIKO zu HD vs. MF-59 Adj:**<br>**Die verfügbaren Daten zur relativen Wirksamkeit von MF-59 adjuvantierten vs. HD Influenza-Impfstoffen bezieht sich auf eine nicht randomisierte Beobachtungsstudien. Daten zu Sicherheit beziehen sich auf einen RCT. Die Vertrauenswürdigkeit der Evidenz zur Wirksamkeit und Sicherheit wird von der STIKO als *niedrig (low)* eingeschätzt.** |
| **GESAMTEINSCHÄTZUNG: Weitere Studien zur Präzisierung der Effektivität und Sicherheit wären wünschenswert.** | |

## Akzeptanz der Influenza-Impfung bei Personen ≥ 60 Jahre

### EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN

- Generell werden Impfung im Erwachsenenalter in Deutschland eher mäßig gut angenommen.
  - Impfquote für saisonale Influenza-Impfung lag im 1. Quartal 2022 bei Personen ≥ 60 Jahren bei 43,3%.
    - Impfquote steigt mit dem Alter an.
    - In der Saison 2021/22 betrug die Impfquote in den Altersgruppen 60 – 69, 70 – 79 und 80 Jahre und älter 34,8%, 48,9% und 51,8%.
- Gründe für die niedrige Akzeptanz der saisonalen Influenza-Impfung bei Personen ≥ 60 Jahre sind unter anderem die Unterschätzung der Schwere einer möglichen Influenza-Infektion, die zuweilen schlechte Wirksamkeit der Impfung in dieser Altersgruppe, Unverträglichkeiten im Rahmen früherer Impfungen, logistische Barrieren sowie die notwendige Wiederholung der jährlichen Impfung vor jeder Saison.

| | |
|---|---|
| EINSCHÄTZUNG DER STIKO zu HD oder MF-59 Adj. vs. SD: **Im Vergleich zum Standardimpfstoff könnte vor allem die leicht erhöhte Reaktogenität eine Hürde bei der Impfakzeptanz von HD- und MF-59 adjuvantierten Impfstoffen darstellen. Hier ist insbesondere eine gute Aufklärung über die verbesserte Wirksamkeit zur Verhinderung von schweren Influenza-Infektionen wichtig.** | EINSCHÄTZUNG DER STIKO zu HD vs. MF-59 Adj: **Mit der Erweiterung der Influenza-Empfehlung auf die Verwendung des HD- oder des MF-59 adjuvantierten Impfstoffs stehen somit zwei Impfstoffarten zur Anwendung bei Personen ≥ 60 Jahren zur Verfügung. Dies könnte zu einer besseren Akzeptanz in der entsprechenden Altersgruppe führen.** |

GESAMTEINSCHÄTZUNG: **Insgesamt ist für die STIKO eine umfangreiche und umfassende Aufklärung über die empfohlenen Impfungen im Erwachsenenalter von großer Bedeutung, damit gerade in dieser Altersgruppe die Impfquoten gesteigert und somit schwere Krankheitsverläufe, Hospitalisierungen und Tod verhindert werden können.**

## Nutzen/Risiko Abwägung zur Erreichung der Impfziele

### EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN

| | **HD- und MF-59 adjuvantierte Influenza-Impfstoffe im Vergleich zum Standardimpfstoff** | **HD- vs. MF-59 adjuvantierte Influenza-Impfstoffe (head-to-head)** |
|---|---|---|
| **positive Effekte** | verbesserte Wirksamkeit zur Verhinderung von Influenza-Erkrankungen und deren Folgen (Hospitalisierung, Tod) bei Personen ≥ 60 Jahre (Confidence of Evidence (CoE): moderat bis niedrig). | Gleichwertige Wirksamkeit zur Verhinderung von Influenza-Erkrankungen und deren Folgen (Hospitalisierung, Tod) bei Personen ≥ 60 Jahre (CoE: niedrig). |
| **negative Effekte** | kein Risiko für eine höhere Zahl an SAEs nach Impfung mit HD oder MF-59 vs. SD (CoE: niedrig)<br><br>leicht erhöhte Rate an transienten lokalen und systemischen Reaktionen | Leicht erhöhtes Risiko für eine höhere Zahl an SAEs nach Impfung mit MF-59 adjuvantierten Impfstoffen (CoE: niedrig)<br><br>kein Risiko für eine höhere Zahl an mit der HD oder MF-59 Impfung im Zusammenhang stehenden SAEs nach Impfung (CoE: niedrig)<br><br>vergleichbare Rate an transienten lokalen und systemischen Reaktionen |

| | | |
|---|---|---|
| **Risiko-Nutzen-Abwägung:** | Positiv Effekte überwiegen deutlich mögliche negative Effekte der Impfung | Beide Impfstoffe werden nach derzeitiger Datenlage als gleichwertig geeignet zum Erreichen des Impfziels angesehen. |

**GESAMTEINSCHÄTZUNG DER STIKO: Die Impfung mit den HD- oder MF-59 adjuvantierten Influenza-Impfstoffen wird in der Gesamtschau als wirksam und sicher für die Altersgruppe der ≥ 60-Jährigen betrachtet. Vor diesem Hintergrund bewertet die STIKO das Nutzen/Risiko-Verhältnis einer Impfung als positiv. Für die AG überwiegen mehrheitlich die positiven Effekte der Impfung mit einem der beiden Impfstoffe die möglichen negativen Effekte.**

## Ressourcen-Effizienz einer Influenza-Impfung mit HD- oder MF-59 adjuvantiertem Impfstoff bei Personen ≥ 60 Jahre

### EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN

**Überlegungen zu wirtschaftlich/ökonomischen Ressourcen:**

- Verwendet wurde eine gesundheitsökonomische Analyse, die für die Empfehlung 2021 generisch die wirkungsverstärkten Influenza-Impfstoff adressierte und auf einem altersstratifizierten Transmissionsmodell aufbaut [61]
- Bei einer konservativen Annahme einer relativen Effektivität der wirkungsverstärkten Impfstoffe im Vgl. zu den konventionellen Influenza-Impfstoffen von 15% sind die wirkungsverstärkten Influenza-Impfstoffe bei einem um bis zu ca. 20% höheren Preis aus gesellschaftlicher Sicht kosteneinsparend
- Bei einem doppelt so hohen Impfstoffpreis im Vergleich zu den herkömmlichen Influenza-Impfstoffen läge das inkrementellen Kosten-Effektivitätsverhältnis bei unter 50.000 €/QALY
- Eine höhere relative Effektivität führt zu höherer Effizienz.
- Aufgrund der Annahme der gleichbleibenden Impfquoten, d.h. dieselben Personen im Alter von ≥ 60 Jahren wechseln lediglich den verwendeten Impfstoff, lassen sich mathematisch keine numbers-needed-to-vaccinate (NNV) berechnen.

| | |
|---|---|
| **EINSCHÄTZUNG DER STIKO zu HD oder MF-59 Adj. vs. SD: Eine Impfung mit wirkungsverstärkten Influenza-Impfstoffen im Vergleich zum SD Influenza-Impfstoffen kann bei Personen im Alter von ≥ 60 Jahren unter plausiblen Annahmen zur relativen Effektivität und zu den Impfstoffpreisen kosteneffektiv sein.** | **EINSCHÄTZUNG DER STIKO zu HD vs. MF-59 Adj: Je nach Impfstoffpreis bei gleichbleibenden weiteren Faktoren kann eine Impfung mit dem MF-59 adjuvantierten im Vergleich zum HD Impfstoff kosteneffektiv oder sogar kostensparend sein.** |

**GESAMTEINSCHÄTZUNG: Mit einer aktualisierten Empfehlung der STIKO für eine jährliche Impfung gegen die saisonale Influenza für alle Personen im Alter von ≥ 60 Jahren mit einem inaktivierten Influenza-Hochdosis-Impfstoff oder einem MF-59 adjuvantierten Influenzaimpfstoff greift das in der Schutzimpfungs-Richtlinie erwähnte und im SGB V festgelegte Wirtschaftlichkeitsgebot. Die Entscheidungen der STIKO hängen primär nicht von ökonomischen Aspekten ab.**

## Ethische Aspekte zur Influenza-Impfung

### EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN

**Verteilung von Nutzen und Risiken der Impfung in der Bevölkerung:**

- Durch die aktive Immunisierung mit einem Influenza-Impfstoff wird allen Personen ≥ 60 Jahren die Möglichkeit gegeben, sich vor einer möglicherweise schwer verlaufenden Influenza-Infektion zu schützen.
- Neben dem individuellen Schutz jeder einzelnen geimpften Person wird auch die Belastung des stationären wie ambulanten medizinischen Bereiches reduziert.
- Der Zugang zur Impfung ist durch die Gabe im hausärztlichen Bereich und Apotheken niederschwellig möglich.
- Sozialökonomische Aspekte spielen eine untergeordnete Rolle, da (vorbehaltlich einer positiven Entscheidung des G-BA) die Impfung für die empfohlenen Personengruppen durch die gesetzlichen Krankenkassen übernommen werden wird.
- Die Nutzen-Risiko-Abwägung für Personen ≥ 60 Jahren fällt deutlich zugunsten des Nutzens aus. In dieser Altersgruppe werden sehr viel mehr RSV-bedingte Hospitalisierungen und Todesfälle aufgrund als Folge einer

Influenza-Infektion verhindert als schwere unerwünschte Arzneimittelwirkungen (UAW), die möglicherweise mit der Impfung in Verbindung stehen auftreten.

| | |
|---|---|
| **EINSCHÄTZUNG DER STIKO zu HD oder MF-59 Adj. vs. SD: Eine Änderung der Standardimpfempfehlung wird für Personen ≥ 60 Jahre aus ethischer Perspektive aufgrund der besseren Wirksamkeit sowie der erweiterten Wahlmöglichkeit als positiv beurteilt.** | **EINSCHÄTZUNG DER STIKO zu HD vs. MF-59 Adj: Eine Änderung der Standardimpfempfehlung wird für Personen ≥ 60 Jahre aus ethischer Sicht aufgrund der erweiterten Wahlmöglichkeit als positiv beurteilt.** |

**GESAMTEINSCHÄTZUNG: Insgesamt werden wenig Änderungen (weder positive noch negative) im Hinblick auf den öffentlichen Zugang zur Impfung für Personen ≥ 60 Jahre erwartet.**

## Monitoring und Umsetzbarkeit der Empfehlung

### EVIDENZ & ZUSÄTZLICHE ÜBERLEGUNGEN

- Monitoring der Impfquoten im ambulanten Bereich via KV-Impfsurveillance, bei der Abrechnungsdaten zu Impfungen und Immunisierungsprogrammen von den Kassenärztlichen Vereinigungen dazu genutzt werden können, bundesweite Impf- sowie Immunisierungsquoten bei gesetzlich krankenversicherten Personen (ca. 85 % der deutschen Bevölkerung) zu bestimmen
- Sicherheitsmonitoring zur Erfassung von unerwünschter Arzneimittelwirkungen (UAW) ist am Paul-Ehrlich-Institut (PEI) etabliert.
- Eine breite Aufklärung der Zielpopulation ist wünschenswert, um ein möglichst hohe Impfquote zu erreichen.
- Impfung wird im hausärztlichen Sektor angeboten, Umsetzung wird als unproblematisch angesehen.
- Etabliertes System der hausärztlichen Versorgung für die Altersgruppe der ≥ 60-Jährigen.
- Koadministration mit COVID-19 und RSV-Impfstoffen möglich

**GESAMTEINSCHÄTZUNG STIKO: Die Implementierung und das Monitoring der Änderung der Influenza Standardimpfempfehlung für Personen ≥ 60 Jahre in den etablierten Strukturen wird als unproblematisch beurteilt.**

*Table 9: Judgments to the question of the evidence to decision tool of the STIKO* ***for high dose or MF-59 adjuvanted versus standard dose influenza vaccines.***

| Question of the evidence to decision tool | JUDGEMENTS | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM**<br>Is the problem/topic of public health importance? | No | Probably no | Probably yes | Yes | | Varies | Don't know |
| **DESIRABLE EFFECTS**<br>Are the desirable outcomes of the intervention frequent, high, and/or long-lasting? | Trivial | Small | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS**<br>Are the undesirable outcomes rare, mild, and temporary**?** | Large | Moderate | Small | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE**<br>What is the overall certainty of evidence for the investigated intervention? | Very low | Low | Moderate | High | | | No included studies |
| **PREFERENCES AND VALUES (ACCEPTABILITY)**<br>How does the target population feel about the ratio of desirable and undesirable effects? | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS**<br>Do the desirable effects outweigh the undesirable effects so that immunization goal can be achieved? | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES**<br>Is vaccination a reasonable and efficient allocation of resources to achieve immunization goal? | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **EQUITY/ETHICAL CONSIDERATIONS**<br>Would the equity be increased or reduced in the public health system? | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **FEASIBILITY**<br>Is it feasible to implement the (new) vaccination strategy? | No | Probably no | Probably yes | Yes | | Varies | Don't know |

*Table 10: Judgments to the question of the evidence to decision tool of the STIKO* ***for high dose versus MF-59 adjuvanted influenza vaccines.***

| Question of the evidence to decision tool | JUDGEMENTS | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM**<br>Is the problem/topic of public health importance? | No | Probably no | Probably yes | Yes | | Varies | Don't know |
| **DESIRABLE EFFECTS**<br>Are the desirable outcomes of the intervention frequent, high, and/or long-lasting? | Trivial | Small | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS**<br>Are the undesirable outcomes rare, mild, and temporary**?** | Large | Moderate | Small | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE**<br>What is the overall certainty of evidence for the investigated intervention? | Very low | Low | Moderate | High | | | No included studies |
| **PREFERENCES AND VALUES (ACCEPTABILITY)**<br>How does the target population feel about the ratio of desirable and undesirable effects? | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS**<br>Do the desirable effects outweigh the undesirable effects so that immunization goal can be achieved? | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES**<br>Is vaccination a reasonable and efficient allocation of resources to achieve immunization goal? | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **EQUITY/ETHICAL CONSIDERATIONS**<br>Would the equity be increased or reduced in the public health system? | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **FEASIBILITY**<br>Is it feasible to implement the (new) vaccination strategy? | No | Probably no | Probably yes | Yes | | Varies | Don't know |

## 10. Referenzen


1. European Centre for Disease Prevention and Control (ECDC). *Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory confirmed influenza in individuals aged 18 years and over.* . 2020; Available from: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-systematic-review-efficacy-vaccines.
2. McGovern, I., et al., *Relative vaccine effectiveness of MF59®-adjuvanted vs high-dose trivalent inactivated influenza vaccines for prevention of test-confirmed influenza hospitalizations during the 2017–2020 influenza seasons.* International Journal of Infectious Diseases, 2024: p. 107160.
3. European Centre for Disease Prevention and Control, *Systematic review of the efficacy, effectiveness and safety of newer and enhanced seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals aged 18 years and over*. Stockholm: ECDC; 2024.
4. Balasubramani, G.K., et al., *Relative effectiveness of high dose versus standard dose influenza vaccines in older adult outpatients over four seasons, 2015-16 to 2018-19.* Vaccine, 2020. **38**(42): p. 6562-6569.
5. Doyle, J.D., et al., *Relative and Absolute Effectiveness of High-Dose and Standard-Dose Influenza Vaccine Against Influenza-Related Hospitalization Among Older Adults-United States, 2015-2017.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2021. **72**(6): p. 995-1003.
6. Klein, N.P., et al., *Vaccine effectiveness of cell-culture relative to egg-based inactivated influenza vaccine during the 2017-18 influenza season.* PloS one, 2020. **15**(2): p. e0229279.
7. Martin, E.T., et al., *Low Influenza Vaccine Effectiveness Against A(H3N2)-Associated Hospitalizations in 2016-2017 and 2017-2018 of the Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN).* The Journal of infectious diseases, 2021. **223**(12): p. 2062-2071.
8. Zimmerman, R.K., et al., *Vaccine effectiveness of recombinant and standard dose influenza vaccines against influenza related hospitalization using a retrospective test-negative design.* Vaccine, 2023.
9. Hsiao, A., et al., *2322. Effectiveness of Recombinant Influenza Vaccine vs. Standard Dose Inactivated Influenza Vaccines Against Hospitalized Influenza-Related Outcomes in Adults: A Cluster Randomized Trial.* Open Forum Infectious Diseases, 2022. **9**(Supplement_2).
10. Domnich, A., et al., *Relative effectiveness of the adjuvanted vs non-adjuvanted seasonal influenza vaccines against severe laboratory-confirmed influenza among hospitalized Italian older adults.* International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases, 2022. **125**: p. 164-169.
11. Van Buynder, P.G., et al., *The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly.* Vaccine, 2013. **31**(51): p. 6122-6128.

12. Mira-Iglesias, A., et al., *Influenza vaccine effectiveness against laboratory-confirmed influenza in hospitalised adults aged 60 years or older, Valencia Region, Spain, 2017/18 influenza season.* Eurosurveillance, 2019. **24**(31).
13. Pebody, R., et al., *Protection provided by influenza vaccine against influenza-related hospitalisation in ≥65 year olds: Early experience of introduction of a newly licensed adjuvanted vaccine in England in 2018/19.* Vaccine, 2020. **38**(2): p. 173-179.
14. Pebody, R.G., et al., *End of season influenza vaccine effectiveness in primary care in adults and children in the United Kingdom in 2018/19.* Vaccine, 2020. **38**(3): p. 489-497.
15. Bellino, S., et al., *Moderate influenza vaccine effectiveness against A(H1N1)pdm09 virus, and low effectiveness against A(H3N2) subtype, 2018/19 season in Italy.* Expert Review of Vaccines, 2019. **18**(11): p. 1201-1209.
16. Kissling, E., et al., *Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): I-move multicentre case control studies at primary care and hospital levels in Europe.* Eurosurveillance, 2017. **22**(7).
17. Rondy, M., et al., *Low 2016/17 season vaccine effectiveness against hospitalised influenza A(H3N2) among elderly: Awareness warranted for 2017/18 season.* Eurosurveillance, 2017. **22**(41).
18. Rondy, M., et al., *2015/16 seasonal vaccine effectiveness against hospitalisation with influenza a(H1N1)pdm09 and B among elderly people in Europe: Results from the I-MOVE+ project.* Eurosurveillance, 2017. **22**(30).
19. DiazGranados, C.A., et al., *Efficacy of high-dose versus standard-dose influenza vaccine in older adults.* New England Journal of Medicine, 2014. **371**(7): p. 635-645.
20. Bruxvoort, K.J., et al., *Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017–2018.* Vaccine, 2019. **37**(39): p. 5807-5811.
21. Dunkle, L.M., et al., *Efficacy of recombinant influenza vaccine in adults 50 years of age or older.* New England Journal of Medicine, 2017. **376**(25): p. 2427-2436.
22. Caldera, F., et al., *Immunogenicity of High Dose Influenza Vaccine for Patients with Inflammatory Bowel Disease on Anti-TNF Monotherapy: A Randomized Clinical Trial.* Inflammatory bowel diseases, 2020. **26**(4): p. 593-602.
23. Chen, J.-Y., et al., *Immunogenicity and safety of high-dose quadrivalent influenza vaccine in older adults in Taiwan: A phase III, randomized, multi-center study.* Vaccine, 2022. **40**(45): p. 6450-6454.
24. Layton, J.B., et al., *Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease.* Vaccine, 2020. **38**(33): p. 5178-5186.
25. Pepin, S., et al., *Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized*

*Phase III trial.* Human vaccines & immunotherapeutics, 2021. **17**(12): p. 5475-5486.
26. Sanchez, L., et al., *Immunogenicity and safety of high-dose quadrivalent influenza vaccine in Japanese adults >=65 years of age: a randomized controlled clinical trial.* Human vaccines & immunotherapeutics, 2020. **16**(4): p. 858-866.
27. Pillsbury, A.J., et al., *Comparative Postmarket Safety Profile of Adjuvanted and High-Dose Influenza Vaccines in Individuals 65 Years or Older.* JAMA network open, 2020. **3**(5): p. e204079.
28. Schmader, K.E., et al., *Safety, Reactogenicity, and Health-Related Quality of Life After Trivalent Adjuvanted vs Trivalent High-Dose Inactivated Influenza Vaccines in Older Adults: A Randomized Clinical Trial.* JAMA network open, 2021. **4**(1): p. e2031266.
29. de Lusignan, S., et al., *Adverse Events of Interest Following Influenza Vaccination in the First Season of Adjuvanted Trivalent Immunization: Retrospective Cohort Study.* JMIR public health and surveillance, 2022. **8**(3): p. e25803.
30. Hansen, J., et al., *Safety of Recombinant Influenza Vaccine Compared to Inactivated Influenza Vaccine in Adults: An Observational Study.* Open forum infectious diseases, 2020. **7**(6): p. ofaa179.
31. Hsiao, A., et al., *Safety of recombinant quadrivalent influenza vaccine compared to inactivated influenza vaccine in Chinese adults: An observational study.* Vaccine, 2022. **40**(5): p. 774-779.
32. Cowling, B.J., et al., *Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial.* Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 2020. **71**(7): p. 1704-1714.
33. de Bruijn, I.A., et al., *The virosomal influenza vaccine Invivac®: Immunogenicity and tolerability compared to an adjuvanted influenza vaccine (Fluad®) in elderly subjects.* Vaccine, 2006. **24**(44-46): p. 6629-6631.
34. Durando, P., et al., *Safety and immunogenicity of two influenza virus subunit vaccines, with or without MF59 adjuvant, administered to human immunodeficiency virus type 1-seropositive and -seronegative adults.* Clinical and Vaccine Immunology, 2008. **15**(2): p. 253-259.
35. Frey, S., et al., *Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults.* Vaccine, 2003. **21**(27-30): p. 4234-4237.
36. Gasparini, R., et al., *Increased immunogenicity of the MF59-adjuvanted influenza vaccine compared to a conventional subunit vaccine in elderly subjects.* European Journal of Epidemiology, 2001. **17**(2): p. 135-140.
37. Li, R., et al., *Safety and immunogenicity of an MF59™-adjuvanted subunit influenza vaccine in elderly Chinese subjects.* Immunity and Ageing, 2008. **5**.
38. Minutello, M., et al., *Safety and immunogenicity of an inactivated subunit influenza virus vaccine combined with MF59 adjuvant emulsion in elderly*

*subjects, immunized for three consecutive influenza seasons.* Vaccine, 1999. **17**(2): p. 99-104.
39. Ruf, B.R., et al., *Open, randomized study to compare the immunogenicity and reactogenicity of an influenza split vaccine with an MF59-adjuvanted subunit vaccine and a virosome-based subunit vaccine in elderly.* Infection, 2004. **32**(4): p. 191-198.
40. Scheifele, D.W., et al., *Safety, immunogenicity, and tolerability of three influenza vaccines in older adults: Results of a randomized, controlled comparison.* Human Vaccines and Immunotherapeutics, 2013. **9**(11): p. 2460-2473.
41. Seo, Y.B., et al., *Comparison of the immunogenicity and safety of the conventional subunit, MF59-adjuvanted, and intradermal influenza vaccines in the elderly.* Clinical and Vaccine Immunology, 2014. **21**(7): p. 989-996.
42. Sindoni, D., et al., *Comparison between a conventional subunit vaccine and the MF59-adjuvanted subunit influenza vaccine in the elderly: An evaluation of the safety, tolerability and immunogenicity.* Journal of Preventive Medicine and Hygiene, 2009. **50**(2): p. 121-126.
43. Couch, R.B., et al., *Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects.* Vaccine, 2007. **25**(44): p. 7656-7663.
44. DiazGranados, C.A., et al., *Safety and immunogenicity of high-dose trivalent inactivated influenza vaccine in adults 50-64 years of age.* Vaccine, 2015. **33**(51): p. 7188-7193.
45. Falsey, A.R., et al., *Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older.* Journal of Infectious Diseases, 2009. **200**(2): p. 172-180.
46. Keitel, W.A., et al., *Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons.* Archives of Internal Medicine, 2006. **166**(10): p. 1121-1127.
47. Tsang, P., et al., *Immunogenicity and safety of Fluzone® intradermal and high-dose influenza vaccines in older adults ≥65 years of age: A randomized, controlled, phase II trial.* Vaccine, 2014. **32**(21): p. 2507-2517.
48. Noh, J.Y., et al., *Randomized, single-blind, active-controlled phase I clinical trial to evaluate the immunogenicity and safety of GC3114 (high-dose, quadrivalent influenza vaccine) in healthy adults.* Vaccine, 2019. **37**(36): p. 5171-5176.
49. Pillet, S., et al., *Immunogenicity and safety of a quadrivalent plant-derived virus like particle influenza vaccine candidate—Two randomized Phase II clinical trials in 18 to 49 and 50 years old adults.* PLoS ONE, 2019. **14**(6).
50. Ehrlich, H.J., et al., *Clinical development of a Vero cell culture-derived seasonal influenza vaccine.* Vaccine, 2012. **30**(29): p. 4377-4386.
51. Frey, S., et al., *Clinical efficacy of cell culture–derived and egg-derived inactivated subunit influenza vaccines in healthy adults.* Clin Infect Dis, 2010. **51**(9): p. 997-1004.

52. Groth, N., et al., *Safety, tolerability and immunogenicity of a mammalian cell-culture-derived influenza vaccine: a sequential Phase I and Phase II clinical trial.* Vaccine, 2009. **27**(5): p. 786-91.
53. Halperin, S.A., et al., *Safety and immunogenicity of a trivalent, inactivated, mammalian cell culture-derived influenza vaccine in healthy adults, seniors, and children.* Vaccine, 2002. **20**(7-8): p. 1240-7.
54. Song, J.Y., et al., *Immunogenicity and safety of a cell culture-derived inactivated trivalent influenza vaccine (NBP607): A randomized, double-blind, multi-center, phase 3 clinical trial.* Vaccine, 2015. **33**(41): p. 5437-5444.
55. Szymczakiewicz-Multanowska, A., et al., *Safety and immunogenicity of a novel influenza subunit vaccine produced in mammalian cell culture.* J Infect Dis, 2009. **200**(6): p. 841-8.
56. Dunkle, L.M., et al., *Randomized comparison of immunogenicity and safety of quadrivalent recombinant versus inactivated influenza vaccine in healthy adults 18-49 years of age.* Journal of Infectious Diseases, 2017. **216**(10): p. 1219-1226.
57. Baxter, R., et al., *Evaluation of the safety, reactogenicity and immunogenicity of FluBlok® trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50-64 years of age.* Vaccine, 2011. **29**(12): p. 2272-2278.
58. Izikson, R., et al., *Randomized comparison of the safety of Flublok(®) versus licensed inactivated influenza vaccine in healthy, medically stable adults ≥ 50 years of age.* Vaccine, 2015. **33**(48): p. 6622-8.
59. Keitel, W.A., et al., *Comparative immunogenicity of recombinant influenza hemagglutinin (rHA) and trivalent inactivated vaccine (TIV) among persons ≥65 years old.* Vaccine, 2009. **28**(2): p. 379-385.
60. Treanor, J.J., et al., *Dose-related safety and immunogenicity of a trivalent baculovirus-expressed influenza-virus hemagglutinin vaccine in elderly adults.* Journal of Infectious Diseases, 2006. **193**(9): p. 1223-1228.
61. Weidemann, F., et al., *Is the impact of childhood influenza vaccination less than expected: a transmission modelling study.* BMC Infectious Diseases, 2017. **17**(1): p. 258.