

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

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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 • high-dose trivalent or quadrivalent inactivated vaccine • cell-based trivalent or quadrivalent inactivated vaccine • recombinant trivalent or quadrivalent HA vaccine • 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.

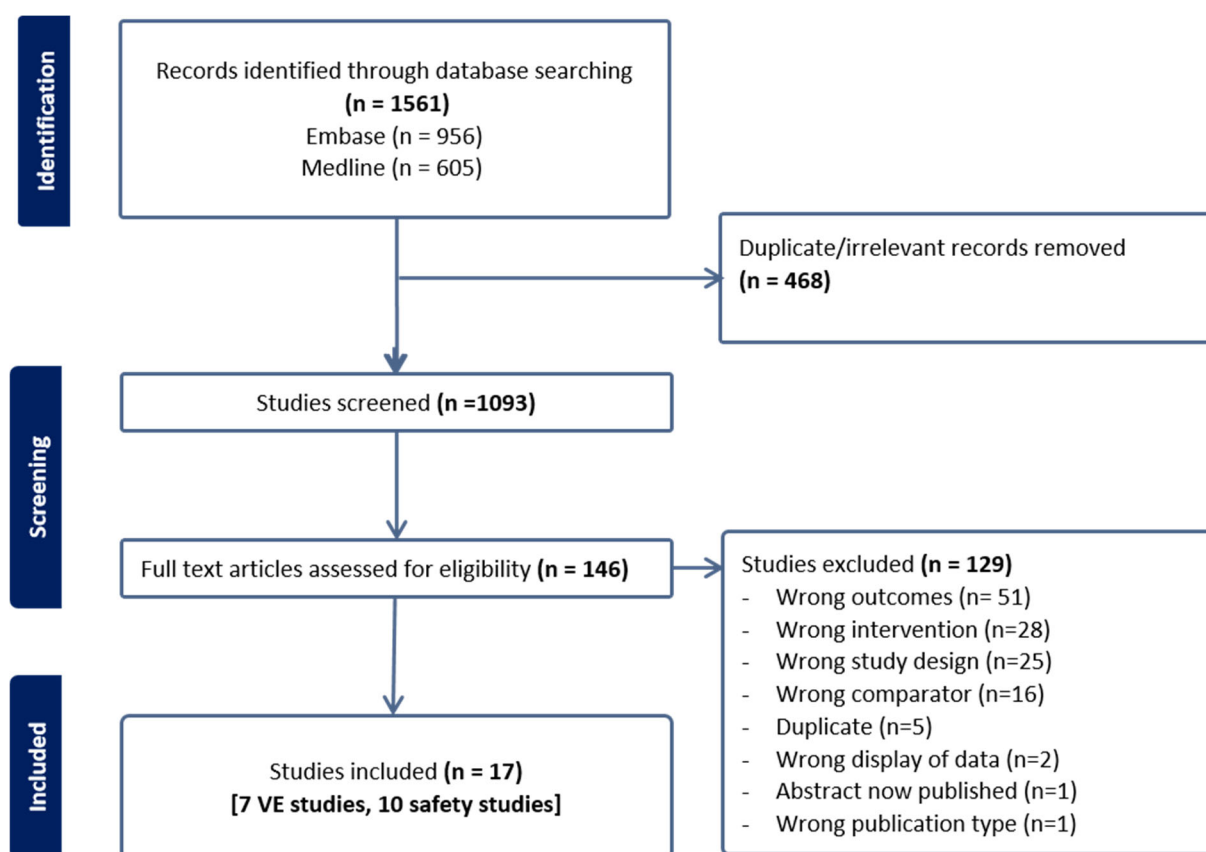


Figure 1: Flow diagram of update search 24th of July 2023

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 conducted 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].

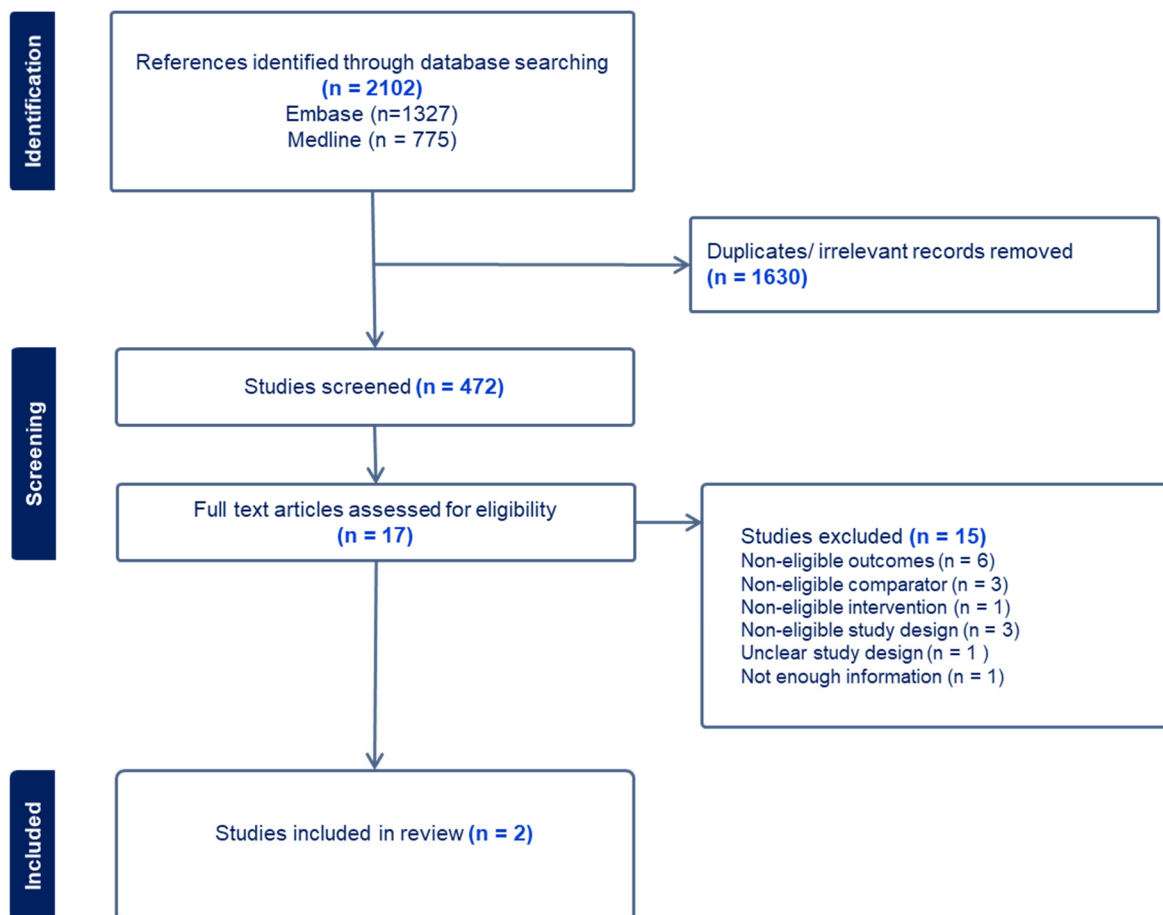


Figure 2: Flow diagram of update search 2nd of September 2024

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 Shamy, 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., Bicler, 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/4v)	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

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Balasubramani 2020								
	Klein 2020								
	Zimmerman 2023								

Domains:

D1: Bias due to confounding.

D2: Bias due to selection of participants.

D3: Bias in classification of interventions.

D4: Bias due to deviations from intended interventions.

D5: Bias due to missing data.

D6: Bias in measurement of outcomes.

D7: Bias in selection of the reported result.

Judgement

 Moderate

 Low

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

Outcome: Influenza-associated hospitalisation (Laboratory confirmed)

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Domnich 2022								
	Doyle 2020								
	Martin 2020								

Domains:

D1: Bias due to confounding.

D2: Bias due to selection of participants.

D3: Bias in classification of interventions.

D4: Bias due to deviations from intended interventions.

D5: Bias due to missing data.

D6: Bias in measurement of outcomes.

D7: Bias in selection of the reported result.

Judgement

 Moderate

 Low

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)

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	de Lusignan 2021	!	-	+	+	-	+	-	!
	Hansen 2020	X	+	+	+	-	+	-	X
	Layton 2020	-	+	+	+	-	+	-	-
	Pillsbury 2020	!	-	+	+	X	-	-	!

Domains:

D1: Bias due to confounding.

D2: Bias due to selection of participants.

D3: Bias in classification of interventions.

D4: Bias due to deviations from intended interventions.

D5: Bias due to missing data.

D6: Bias in measurement of outcomes.

D7: Bias in selection of the reported result.

Judgement

! Critical

X Serious

- Moderate

+

Low

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)

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	de Lusignan 2021	!	-	+	+	-	+	-	!
	Hansen 2020 (inpatient/ ED)	X	+	+	+	-	+	-	X
	Hansen 2020 (outpatient)	X	+	+	+	-	+	-	X
	Hsaio 2022	-	+	+	+	-	+	-	-
	Layton 2020	-	+	+	+	-	+	-	-
	Pillsbury 2020	!	-	+	+	X	-	-	!

Domains:

D1: Bias due to confounding.

D2: Bias due to selection of participants.

D3: Bias in classification of interventions.

D4: Bias due to deviations from intended interventions.

D5: Bias due to missing data.

D6: Bias in measurement of outcomes.

D7: Bias in selection of the reported result.

Judgement

! Critical

X Serious

- Moderate

+ Low

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

Outcome: SAE – randomized controlled trials (RCT)

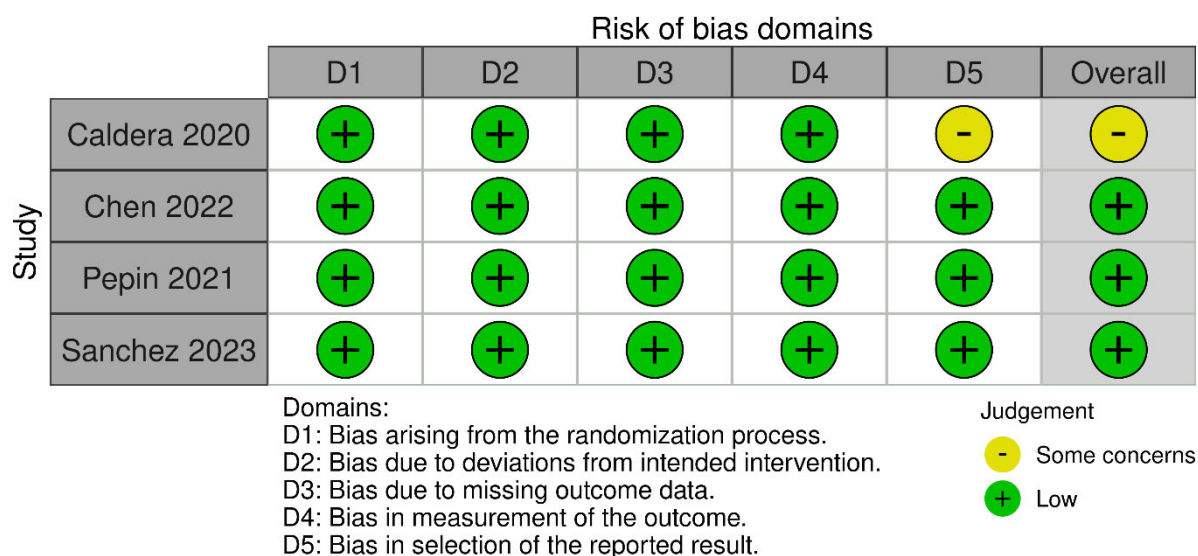


Figure 7: Risk of bias in RCT safety-studies (assessed with RoB2); outcome: SAE (serious adverse events)

Outcome: Fever - RCT

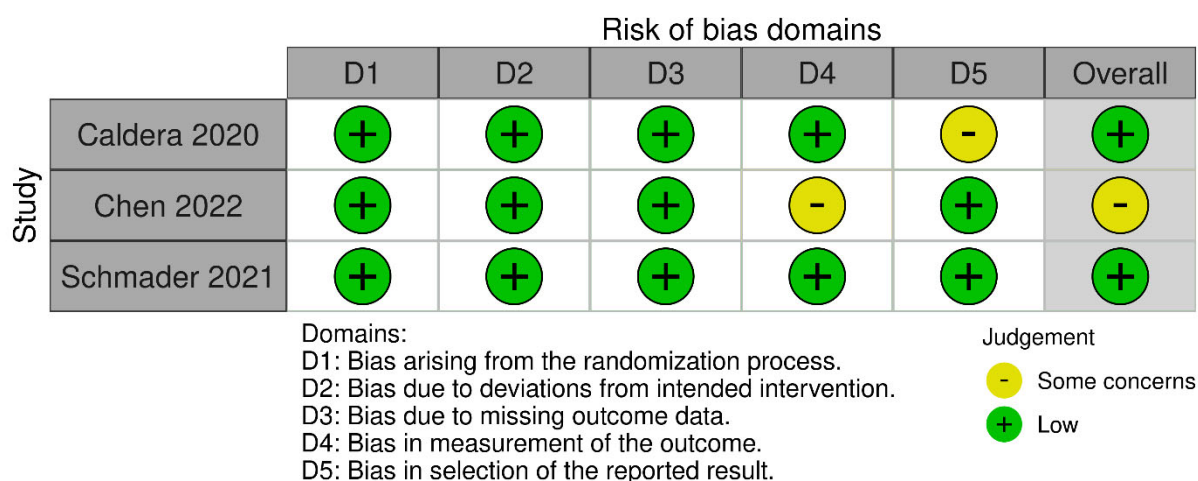


Figure 8: Risk of bias in RCT safety-studies (assessed with RoB 2); outcome: Fever

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 № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		With standard influenza vaccine	MF59- adjuvanted influenza vaccine	Difference		
Laboratory confirmed influenza № of participants: 10,492 (7 observational studies)	rVE-range: -30 (-146 to 31) to 88 (51 to 100)	N. A.	N. A.	N.A.	⊕⊕○○ 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) № of participants: 512 (1 observational study)	rVE 59.2 (14.6 to 80.5)	N.A.	N.A.	N.A.	⊕⊕⊕○ 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) № of participants: 8356 (3 RCTs)	RR 0.95 (0.19 to 4.72)	0.1%	0.1% (0 to 0.3)	0.0% fewer (0.1 fewer to 0.3 more)	⊕⊕○○ 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 № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		With standard influenza vaccine	High-dose influenza vaccine	Difference		
Laboratory confirmed influenza (lab confirmed) assessed with: PCR № of participants: 31989 (1 RCT)	rVE 24 (11 to 36)	1.9%	1.4% (1.2 to 1.7)	0.5% fewer (0.7 fewer to 0.2 fewer)	⊕⊕⊕○ Moderate ^a	High-dose influenza vaccines probably slightly reduce laboratory- confirmed influenza infection in adults.
Influenza related hospitalisation (laboratory confirmed) assessed with: PCR № of participants: 1107 (1 NRSI)	rVE 27 (-1 to 48)	N.A.	N.A.	N.A.	⊕⊕○○ 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) № of participants: 9034 (6 RCTs)	RR 1.02 (0.42 to 2.46)	0.2%	0.2% (0.1 to 0.6)	0.0% fewer (0.1 fewer to 0.4 more)	⊕⊕○○ 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 № of participants (studies)	Relative effect (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) assessed with: PCR № of participants: 1,025,097 (2 observational studies)	rVE-range -5.8 (-36.1 to 17.7) to 21.4 (-7.3 to 42.4)	N.A.	N.A.	N.A.	⊕⊕○○ Low ^a	Cell-based influenza vaccines may or may not reduce laboratory- confirmed influenza infection in adults.
Influenza related hospitalisation (laboratory confirmed) assessed with: PCR № of participants: 1741 (1 observational study)	rVE 8.5 (-75.9 to 52.3)	N.A.	N.A.	N.A.	⊕⊕○○ 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) № of participants: 3208 (1 RCT)	RR 0.39 (0.02 to 9.49)	N.A.	N.A.	N.A.	⊕⊕○○ 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 № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		With standard influenza vaccine	With recombinant influenza vaccine	Difference		
Laboratory confirmed influenza (lab confirmed) assessed with: PCR № of participants: 8855 (1 RCT)	rVE 30 (10 to 47)	3.1%	2.2% (1.7 to 2.8)	0.9% fewer (1.5 fewer to 0.3 fewer)	⊕⊕⊕○ Moderate ^a	Recombinant influenza vaccines probably slightly reduce laboratory- confirmed influenza infection in adults.
Influenza related hospitalisation (laboratory confirmed) assessed with: PCR № of participants: 1,630,328 (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) № of participants: 907 (2 RCTs)	RR 3.04 (0.32 to 29.10)	N.A.	N.A.	N.A.	⊕⊕○○ Low ^b	Recombinant influenza vaccines may or may not result in an increase in serious adverse events (SAEs) related to vaccination.
Idiopathic thrombocytopenic purpura № of participants: 42,684 (1 observational study)	OR 0.52 (0.15 to 1.50)	N.A.	N.A.	N.A.	⊕⊕○○ Low ^{c,d}	Recombinant influenza vaccines may or may not result in an decrease in of idiopathic thrombocytopenic purpura related to vaccination.
Narcolepsy/cataplexy № of participants: 305,659 (1 observational study)	OR 0 (0 to 6)	N.A.	N.A.	N.A.	⊕○○○ Very low ^{d,e}	Evidence is uncertain about the effect of recombinant influenza vaccines on narcolepsy/cataplexy related to vaccination.
Guillain-Barré syndrome (GBS) № of participants: 305,659 (1 observational study)	OR 0.00 (0.00 to 16.07)	N.A.	N.A.	N.A.	⊕○○○ 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				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard influenza vaccine	With MF-59 adjuvanted influenza vaccine		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)				
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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)
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Laboratory confirmed death - not reported

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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				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard vaccination	With High-dose influenza vaccine		Risk with standard vaccination	Risk difference with High-dose influenza vaccine

Laboratory confirmed influenza (assessed with: PCR)

Nº 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)
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Laboratory confirmed hospitalisation (assessed with: PCR)

Nº 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

Nº 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)
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Laboratory confirmed death - not reported

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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				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard vaccine	With cell-based influenza vaccine		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%				
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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 --)
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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)
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Laboratory confirmed death - not reported

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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				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard influenza	With recombinant influenza vaccine		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)
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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.				
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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)
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Laboratory confirmed death - not reported

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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)
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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 --)
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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 --)
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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		
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: • Laborbestätigte Influenza • Influenza-bedingte Mortalität (laborbestätigt) • Influenza-bedingte Hospitalisierung (laborbestätigt) • Influenza-assoziierte kardiovaskuläre Erkrankung (laborbestätigt) • Influenza-assoziierte Pneumonie oder untere Atemwegserkrankung (laborbestätigt) • Influenza-like illness (gemäß international akzeptierter Definition, z. B. nach WHO, US CDC, EU)	Sicherheit: • Schwerwiegende unerwünschte Ereignisse (SAE) • Reaktogenität lokal und systemisch, jeglicher Schwere
IMPFZIEL:	Ziel der Impfempfehlung ist die Reduktion schwerer Influenza-assoziiierter 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: ▪ 7 NRSI: variable rVE [-30 (-146 to 31) to 88 (51 to 100)] (2020 review)	▪ MF-59 adjuvanted vaccine: ▪ 1 NRSI: rVE 59% [15 to 81] (2024 SR update)
▪ High-dose (HD) vaccine: ▪ 1 RCT: rVE 24.4% [10 to 37] (2020 review) ▪ Not confirmed by 1 NRCT (rVE: 10% [-15 to 30]) (2024 SR update)	▪ High-dose (HD) vaccine: ▪ 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: ▪ 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) no new data in update → 3 RCT, 2 NRSI	no group differences (2020) no new data in update → 6 RCT, 3 NRSI
Systemic reaction	Fever: RR: 1.97 (2020) no new data in update (2024) → 10 RCT	Headache: RR: 1.4 (2020) RR: 1.0-2.3 in update (2024) → 3 RCT
Systemic reaction	Pain: RR 2.02 (2020) no new data in update (2024) → 12 RCT	Pain: RR: 1.5 (2020) RR: 1.1 to 2.2 in update (2024) → 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 MF-59 vs. HD in Update 2024: RR: 3.01 (95% CI: 0.82 to 11.02), no vaccine related SAE in either group → 1 RCT
Systemic reaction	No data in 2020 review MF-59 vs. HD in Update 2024: Headache, RR: 1.10 [95% CI: 0.73 to 1.66] Fever (any), RR: 0.80 [95% CI: 0.38 to 1.68] → 1 RCT
Systemic reaction	No data in 2020 review MF-59 vs. HD in Update 2024: Pain, RR: 0.85 [95% CI: 0.66 to 1.10] → 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 <i>gering (small)</i> 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 <i>sehr gering (trivial)</i> ein.
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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				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard influenza vaccine	With MF-59 adjuvanted influenza vaccine		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)				
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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)
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Laboratory confirmed death - not reported

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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				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard vaccination	With High-dose influenza vaccine		Risk with standard vaccination	Risk difference with High-dose influenza vaccine

Laboratory confirmed influenza (assessed with: PCR)

Nº 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)
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Laboratory confirmed hospitalisation (assessed with: PCR)

Nº 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

Nº 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)
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Laboratory confirmed death - not reported

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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				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With high dose influenza vaccine	With MF-59 adjuvanted influenza vaccine		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)
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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
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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)
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Laboratory confirmed death - not reported

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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:

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:

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) 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) kein Risiko für eine höhere Zahl an mit der HD oder MF-59 Impfung im Zusammenhang stehenden SAEs nach Impfung (CoE: niedrig) 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.
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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 Is the problem/topic of public health importance?	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS Are the desirable outcomes of the intervention frequent, high, and/or long-lasting?	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS Are the undesirable outcomes rare, mild, and temporary?	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE What is the overall certainty of evidence for the investigated intervention?	Very low	Low	Moderate	High			No included studies
PREFERENCES AND VALUES (ACCEPTABILITY) 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 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 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 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 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 Is the problem/topic of public health importance?	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS Are the desirable outcomes of the intervention frequent, high, and/or long-lasting?	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS Are the undesirable outcomes rare, mild, and temporary?	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE What is the overall certainty of evidence for the investigated intervention?	Very low	Low	Moderate	High			No included studies
PREFERENCES AND VALUES (ACCEPTABILITY) 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 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 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 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 Is it feasible to implement the (new) vaccination strategy?	No	Probably no	Probably yes	Yes		Varies	Don't know

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