Table 3. TIV vaccination in individuals aged 65 years or more

Conclusion on outcomes drawn separately for community setting and care facilities, as available.

Is matched, inactivated influenza vaccine versus placebo effective to prevent influenza infection in individuals aged 65 years or more?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		5 RCTs[1, 2]	4
	Factors decreasing confidence	Limitation in study design	Very serious[2, 3]	- 2
		Inconsistency	Serious[4]	-1
		Indirectness	None serious[5]	0
		Imprecision	None Serious	0
		Publication bias	Serious[6]	-1
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1** (numerical rating 0 but value cannot be <1)
Summary of Findings	**Statement on quality of evidence**			Our confidence in the estimate of effect of influenza vaccination of the elderly on influenza and ILI is low and given the large heterogeneity of settings, outcomes and interventions used in the trials, conclusions are difficult to draw.
	Conclusion			Community Under the condition of high viral circulation (outbreak), matched, inactivated (parenteral) influenza vaccine is more **efficacious than placebo against serologically (and clinically) confirmed influenza** (relative risk of 0.42 (95% CI: 0.23 to 0.74)[7] as well as **against ILI** among healthy elderly resulting in an effectiveness of **43% (95% CI: 21 to 58).**[8] **No effect was shown on all cause mortality** by Allsup et al. 2004 (relative risk of 0.96; 95% CI: 0.1 to 9.19). Care facility setting Under the condition of high viral circulation (outbreak), matched, inactivated influenza vaccine is **more effective than placebo against ILI among healthy elderly** living in a nursing home **(**RR 0.54; 95% CI: 0.37 to 0.80).[9] Two trials conducted in facilities **(independent of outbreak and health status of elderly)** and assessing effects on laboratory-confirmed influenza showed **no individual significant effect** of matched vaccine **on influenza.**[10] Independent of setting (community/facility) and population (with or without underlying health conditions), outbreak: Pooled results of four trials[11] showed a RR of 0.59 (95% CI: 0.47 to 0.73) for ILI, indicating **effectiveness of influenza vaccination against ILI in the elderly.** Pooled estimates of three trials indicate a **efficacy against laboratory-confirmed influenza of 58%** (95% CI 34 to 73%) among the elderly.[12]

NOTES

[1] RCTS by Allsup et al. 2004, Edmondson et al. 1971, Govaert et al. 1994, Rudenko et al. 2000, Stuart et al. 1969 assessed the effects of influenza vaccines in elderly aged 65 years and above, irrespective of vaccine tested, setting, outcome definition, and follow up. The outcomes included effectiveness in preventing influenza, ILI, hospital admissions, complications and mortality. The trials were part of a Cochrane review conducted by Jefferson et al. 2010, but there were major differences in definition of outcomes, settings etc. thus that pooling of data was possible only partly.
The trials were included in the assessment as follows and according to data provided:
Allsup et al. for outcome on laboratory-confirmed influenza, on mortality, and on ILI in community settings (matched, outbreak situation).
Goavert et al. for outcome on laboratory-confirmed influenza and on ILI in community setting (matched, outbreak situation).
Stuart et al. for outcome on ILI in care facility setting, healthy individuals (matched, outbreak situation).
Edmondson et al. for outcome on laboratory-confirmed influenza and on ILI in care facility setting (matched, outbreak situation).
Rudenko et al. for outcome on laboratory-confirmed influenza in care facility setting (matched, non-outbreak situation).

Another systematic review was identified (Vu et al. 2002), but was not included in the grading process due to methodological limitations. The main limitations of that review include the lack of assessment of study quality, the exclusion of studies with small denominators, pooling of studies of different designs, and the overall limited number of studies.
Safety of influenza vaccine was also assessed in RCTs included in the meta-analysis by Jefferson et al. (2010). Pooled estimate indicate that the vaccines induced systemic adverse effects like general malaise, fever, nausea, upper respiratory tract symptoms and headache more frequently than placebo, but no outcome showed statistically significant results (Jefferson et al. 2010). Local adverse events, such as tenderness and sore arm, were significantly more frequent in the treatment arm than in the placebo arm.

[2] A number of case-control and cohort studies evaluated potential effects of influenza vaccination in the elderly. However, they are affected by selection bias resulting from differential uptake of vaccination due to various factors such as socio-economic conditions, anxiety or health status (vaccines might be used more in people of worse health status which would reduce VE whereas those less likely to be vaccinated might be those with terminal illnesses and low socio-economic status which would result in enhanced VE). The non-RCT evidence was not methodologically appropriate, which is exemplified by the finding that there was a high effectiveness of influenza vaccine against all cause mortality (different for RCT pooled estimate, which did not show effectiveness), but ineffectiveness in the prevention of influenza, ILI and pneumonia (pooled estimates from observational studies, Jefferson et al. 2010). This points to the potential of considerable confounding induced by non-randomization and questioning of reliability of these outcome measures as well as to residual heterogeneity across studies.

[3] Selection bias is a concern in some RCTs and may have resulted in a baseline imbalance in systematic differences, e.g. health status, between intervention and control groups. Adequate randomization and allocation concealment was done in two RCTs (Allsup et al. 2004, Govaert et al. 1994) but there was no or unclear allocation concealment in studies by Edmondson et al. 1971, Rudenko et al. 2000 and Stuart et al. 1969. Follow-up time is not specified in Allsup et al. 2004 and Edmondson et al. 1971 and those trials specifying follow-up time gave a range from 41 to 180 days.
No power calculation was made to detect effect modification by age (Govaert et al. 1994) and the external validity might be affected (differences in declining participants and participants).

[4] There is a certain degree of heterogenicity in terms of vaccines tested, settings, follow-up and outcome definitions. Heterogenity was adjusted for in Jefferson et al. (2010) and reflected in pooled estimated presented in the conclusion section but not for all outcomes, pooling was possible.

[5] Non-specific outcomes, namely ILI and all-cause mortality were used in the existing trials and both outcomes are subject to residual confounding (see note 5, table 2b). However, no downgrading was applied since the specific outcome of laboratory-confirmed influenza was available from some of the RCTs and used for evidence grading.

[6] A relationship between data, conclusion drawn, study funding and journal of publication is likely. Analysis by Jefferson et al. (2009, 2010) suggest that higher quality studies were significantly more likely to show concordance between data presented and conclusion but less likely to favour effectiveness.

[7] Goavert et al. 1994. Age-stratification in Goavert et al. 1994 indicates that, except for the age-group above 70 years, all age-groups vaccinated had significantly lower incidence of influenza and ILI.

[8] Pooled results of two trials (Allsup et al. 2004 and Govaert et al. 1994).

[9] Jefferson et al. 2010, based on Stuart et al. 1969

[10] Risk ratio obtained from Jefferson et al. 2010, based on Edmondson et al. 1979: 0.35; 95% CI: 0.12 to 1.06); risk ration obtained from Jefferson et al. 2010, based on Rudenko et al. 2000: 0.50; 95% CI: 0.20 to 1.25. The trial by Rudenko et al. 2000 was not conducted during an outbreak situation!

[11] Allsup et al. 2004, Edmondson et al. 1971, Govaert et al. 1994, Stuart et al. 1969

[12] Edmondson et al. 1979, Govaert et al. 1994, Rudenko et al. 2000

References

Allsup, S.J., et al., *Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomised controlled trial.* Vaccine, 2004. **23**: 639-45.

Edmondson, W.P., Jr., et al., *A comparison of subcutaneous, nasal, and combined influenza vaccination. II. Protection against natural challenge.* American Journal of Epidemiology, 1971. **93**:480-6.

Govaert, T.M., et al., *The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial.* The Journal of the American Medical Association, 1994. **272**:1661-5.

Jefferson, T., et al., Vaccines for preventing influenza in the elderly. Cochrane Database of Systematic Reviews, 2010(2): p. CD004876.

Rudenko, L.G., et al., *Immunogenicity and efficacy of Russian live attenuated and US inactivated influenza vaccines used alone and in combination in nursing home residents.* Vaccine, 2000. **19**:308-18.

Stuart, W.H., et al., *Evaluation of monovalent influenza vaccine in a retirement community during the epidemic of 1965-66.* The Journal of the American Medical Association, 1969. **209**:232-8.

Vu, T., et al., *A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community.* Vaccine, 2002. **20**:1831-6.