CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Secondary Prevention of Stroke
Seventh Edition, 2020
Evidence Table: *Lifestyle & Risk Factor Management (Influenza Infection, Vaccination & Stroke Risk)*

Gladstone D, Poppe A (Writing Group Chairs)
on Behalf of the Canadian Stroke Best Practice Recommendations
Secondary Prevention of Stroke Writing Group and in collaboration with the Canadian Stroke Consortium

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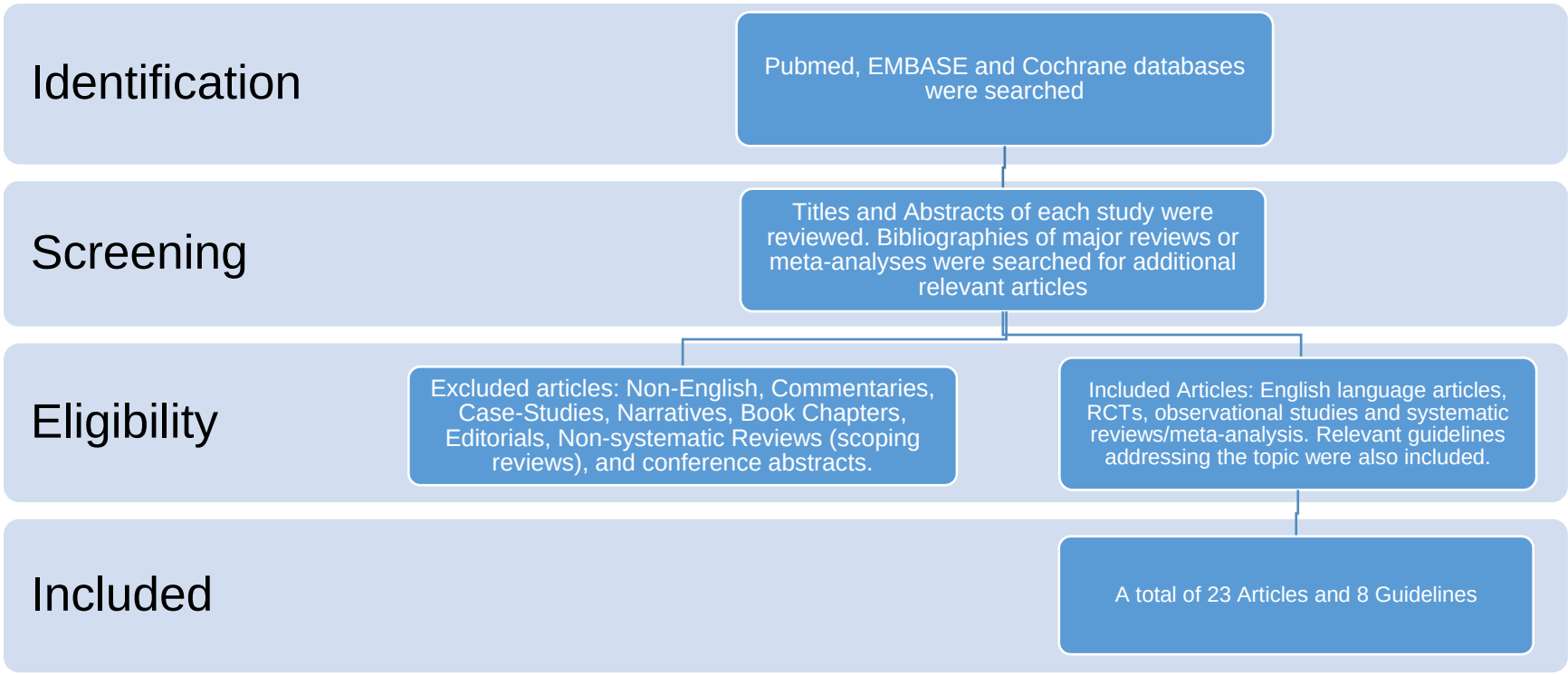
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were search using the terms (“influenza” OR “influenza vaccine” AND “Stroke”). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 23 articles and 8 guidelines were included and were separated into separate categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. **2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.** ***European heart journal* 2019. 00, 1-71. doi:10.1093/eurheartj/ehz425**	Annual influenza vaccination is recommended for patients with chronic coronary syndrome, especially in the elderly. Class of recommendation 1; level of evidence B
National Advisory Committee on Immunization (NACI). Canadian Immunization Guide chapter on influenza and statement on seasonal influenza vaccine for 2016-2017. Ottawa (ON): Public Health Agency of Canada. Available from: www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-eng.php	Influenza vaccination is recommended for all individuals aged 6 months and older (noting product-specific age indications and contraindications), with particular focus on people at high risk of influenza-related complications or hospitalization, including all pregnant women, people capable of transmitting influenza to those at high risk.
Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG. **2017 Comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure** ***Can J Cardiol* 2017;33(11):1342-433.**	Practical tip. Patients at high risk for developing HF should receive annual influenza vaccine and periodic pneumococcal pneumonia immunizations.
Stroke Guidelines	
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke	None

Guideline	Recommendations
Foundation. Section 4 Secondary Prevention	
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical Guidelines for Stroke. 5th Edition 2016, Edinburgh, Scotland	None
Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. **Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke 2014*;45:2160-2236.**	None
New Zealand Clinical Guidelines for Stroke Management 2010, Stroke Foundation of New Zealand, Auckland.	None

Evidence Tables

Temporal Association between Influenza and Stroke/Myocardial Infarction

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Covid-19 and Risk of Stroke					
Merkler et al. 2020 **USA** **Retrospective study**	NA	1,916 adult patients presenting to the Emergency Department (ED) and/or admitted to 2 hospitals between March 4, and May 2, 2020, with confirmed Covid-19. Median age was 64 years, 57% were men. 1,486 adult patients with an ED visit or hospitalization with laboratory-confirmed influenza A or B between January 1, 2016, and May 31, 2018. Median age was 62 years, 45% were men.	The risk of ischemic stroke was compared between the COVID-19 and influenza cohorts.	**Primary outcome:** Acute ischemic stroke	31 patients (1.6%) with Covid-19 had an acute ischemic stroke. The median time from Covid-19 symptoms to stroke onset was 16 days. Stroke symptoms were the presenting complaint in 8 patients (26%), while 23 patients (74%) developed acute ischemic stroke while hospitalized. Inpatient mortality was significantly higher in patients with Covid-19 with ischemic stroke compared with those with Covid-19 without stroke (32% vs.14%, p=0.003). In the influenza cohort, 3 patients (0.2%) had an acute ischemic stroke. After adjustment for age, sex, and race, the odds of acute ischemic stroke were significantly higher in the Covid-19 cohort (OR=7.6; 95% CI, 2.3-25.2)
Li et al. 2020 **China** **Retrospective study** ***Acute cerebrovascular disease following COVID-19: a single center,***	NA	221 patients admitted to a single centre from 16 January 2020 to 29 February 2020 with COVID-19. Mean age was 53.3 years, 40.7% were women.	The characteristics of the 13 patients who developed a stroke were compared with the remainder of the patients in the cohort (n=208)	**Primary outcome:** Stroke	11 (5%) patients developed acute ischemic stroke, 1 (0·5%) developed cerebral venous sinus thrombosis and 1 (0·5%) developed cerebral hemorrhage. Median age was 73·5 years, 46.2% were women. Median duration from COVID-19 onset to stroke was 10 days. Patients with stroke were significantly older 71·6 vs 52·1 years; p<0·05), had more CVD risk factors, including hypertension and diabetes, and had a more severe case of COVID-19. They also had significantly higher levels associated with inflammation (C-reactive

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retrospective, observational study					protein 51·1 vs 12.1 mg/L, p<0·01) and hypercoagulable state (D-dimer 6.9 vs 0.5 mg/L, p<0·001). Patients with stroke were more likely to have liver and kidney injury, with significantly increased aspartate aminotransferase levels, blood urea nitrogen and creatinine levels. Patients were treated with aspirin or clopidogrel (n=6) or enoxaparin (n=5). Of patients with stroke, 5 had died, to date.
Influenza and Risk of Stroke					
Kwong et al. 2018 **Canada** **Case-series design**	NA	332 patients ≥35 years hospitalized for acute MI who had a laboratory-confirmed diagnosis of influenza in the year prior to MI or one year after hospitalization for MI. Median age was 77 years, 52% were men. 24% of patients had a previous MI. 31% had been vaccinated.	The incidence of MI during the risk period was compared with the control period. The risk interval was defined as the 7-day period after influenza diagnosis and the control period as all other time periods (52 weeks before influenza and 51 weeks after). The date of specimen collection served as the date of influenza onset.	**Primary outcome:** Risk of MI	The risk of acute MI during the risk period was significantly higher compared with the control period (20.0 MI admissions per week during the risk interval vs. 3.3 admissions per week during the control interval: IR=6.05, 95% CI 3.86-9.50). The risk of MI was highest 1-3 days prior to influenza diagnosis (IR=6.30, 95% CI 3.25–12.22, vs. 4-7 days IR=5.78, 95% CI 3.17-10.53), with no significantly increased risk with influenza diagnosed 8-28 days previously. No treatment interactions were observed for age, sex, influenza sub type, vaccination status, laboratory methods to identify influenza or previous MI.
Boehme et al. 2018 **USA** **Case-crossover study**	NA	36,975 patients hospitalized for ischemic stroke in any of the non-federal acute care hospitals in California in 2009.	Conditional logistic regression was used to estimate the odds of hospital admission for stroke within 0–15 days, 0–30 days, 0–60, 0–90, 0–180, and 0–365 days after influenza exposure, using data from the California State Inpatient Database of the Healthcare Cost and Utilization Project. Exposure was defined as a visit to the	**Primary outcome:** Risk of ischemic stroke	554 (1.5%) persons had at least one episode of influenza in the 365-day period prior to stroke. The odds of ischemic stroke were increased significantly given prior influenza exposure. Within 15 days OR= 2.88, 95% CI 1.86–4.470 Within 30 days OR= 1.81, 95% CI 1.11–2.92 Within 60 days OR=1.68, 95% CI 1.19–2.38 The odds of ischemic stroke were not

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			emergency department or hospitalization for influenza-like illness within the previous year (risk period) or similar time intervals exactly 1 or 2 years before stroke (control period).		increased significantly from 60-365 days. The risk of stroke was highest among 18-45-year old's with influenza exposure within the previous 15 days (OR= 9.28, 95% CI 1.72–50.2). There was a significant interaction (p= 0.017) with age and influenza. The odds of stroke increased 7% with each 10-year decrease in age (OR per 10-year age decrease= 1.07, 95% CI 1.03–1.35).
Elkind et al. 2011 **US** **Case-crossover study**	NA	5,888 men and women, aged ≥65 years included in the Cardiovascular Health Study without a history of stroke	The risk of stroke given previous hospitalization for infection was examined in 669 incident cases of ischemic stroke by comparing the risk of stroke during the case period (hospitalization for infection within 90, 30, or 14 days before stroke) with 2 equivalent time periods exactly 1 or 2 years before the stroke (control periods). A confirmatory survival analysis was also done for strokes occurring from 1989-2005.	**Primary outcome:** Risk of stroke	Median duration of follow-up was 12.2 years. Of the 669 incident ischemic strokes, 29 were preceded by hospitalization within the previous 90 days for infection during the case period. During the control period, there were 17 hospitalizations for infections. Hospitalization for infection within 90 days was associated with an increased risk of stroke (OR=3.4, 95% CI 1.8–6.5). During the preceding 30 days, there were 11 hospitalizations for infections during the case period and 3 during the control period (OR= 7.3, 95% CI 1.9–40.9). During the preceding 14 days, there were 8 hospitalizations for infections during the case period and 2 during the control period (OR= 8.0, 95% CI 1.6–77.3). In survival analysis, the risk of stroke, adjusted for age, sex, race, diabetes, smoking and internal carotid intima–media thickness, the risk of ischemic stroke was significantly increased with hospitalizations for infections in the preceding 14, 30 and 90 days. (90-day HR=2.4, 95% CI, 1.6 to 3.4).
Toschke et al.	NA	2,874 patients with first-	A multivariate time series analysis	**Primary outcome:**	There were 21,473 influenza cases reported

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2009 **UK** **Retrospective study**		ever stroke (73% ischemic, 20% hemorrhagic) included in the South London Stroke Register between 1995-2004	was used to assess an association between influenza infections and strokes. Time lags of 1 to 5 weeks between preceding influenza and stroke were used to identify the length of increased hazard after an influenza infection	Association between influenza and stroke	during the study period, most of which occurred between the end of December and March. In multivariate analysis, there was a significant association between influenza and first-ever ischemic stroke with time lags of 1 and 2 weeks (both $p < 0.001$), with no association after 3 weeks. There was an association between influenza and hemorrhagic strokes for a time lag of 1, 2, 3 and 4 weeks (all $p <0.001$).
Clayton et al. 2008 **UK** **Case control study**	NA	11,155 cases of first-ever MI and 9,208 cases of first-ever stroke were identified from the IMS Disease Analyzer Mediplus primary care database. Mean age of stroke cases was 76 years, 45% were men. A single control for each case was selected from the same population and were registered in the GP database using the same criteria as the cases	The association between respiratory infection and the onset of stroke and MI was assessed, with models adjusted for the matching factors of year of birth, gender, calendar time (and therefore seasonal variation), and practice. The timing of any respiratory infection was categorized as: 1 –7, 8 – 28, 29 – 91, 92 – 365 days prior to the index date.	**Primary outcomes:** Risk of stroke and MI	There were 855 (9.3%) stroke cases with respiratory infection in the year before the index date compared to 735 (8.0%) controls. The odds of stroke were significantly increased within 7 days of an infection (OR=1.92, 95% CI 1.24– 2.97), and 8-28 days (OR=1.76, 95% CI 1.27–2.45) but not for the other time intervals. The risk was highest within the first 3 days following infection (OR=4.07, 95% CI 1.99–8.34). There were 934 (8.4%) MI cases with respiratory infection in the year before the index date compared to 736 (6.6%) controls. The odds of MI were significantly increased within 7 days of an infection (OR=2.10, 95% CI 1.38– 3.21), and 8-28 days (OR=1.93, 95% CI 1.42–2.63) but not for the other time intervals. The risk was highest in the 3 days following infection (OR=3.75, 95% CI 1.86– 7.56).
Field et al. 2004 **Canada** **Retrospective study**	NA	Patients admitted to Calgary Hospitals from 1994-2001 with a primary diagnosis of stroke	Hospitalizations associated with stroke were retrieved through institutional database and were linked with a viral watch database, whereby cases of influenza (and other viruses) are reported by	**Primary outcome:** Strength and direction of association	The mean stroke occurrence per 100,000 population/week ranged from 20.4 to 24.1. The mean occurrences of influenza A or B ranged from 15.2 to 47.6 per 100,000/week. The mean delay between influenza activity and

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			general practitioners. Regression equations were fitted to examine the relationship between influenza and stroke.		stroke activity was 19.1 weeks for total stroke, 16.3 weeks for ischemic stroke, 3.0 weeks for TIA, 2.8 weeks for ICH and 0.9 weeks for SAH. As influenza rates increased, so did stroke rates. The slope of the β co-efficient for total stroke was 0.63 (95% CI 0.58-0.67) A tripling of the influenza rate was associated with an approximate 6% increase in stroke rate.
Smeeth et al. 2004 **UK** **Within-person case series**	NA	20,486 persons ≥18 years, with first-ever MI and 19,063 persons with a first-ever stroke who received influenza vaccine, included in the United Kingdom General Practice Research Database (GPRD) between 1987-2001.	The risk of stroke or MI among persons who had a respiratory tract infection (based on physician visit) in the preceding 90 days was examined. The incidence of MI and stroke during the exposure period was compared with the non-exposure period. The risk interval was defined as the 90-day period after influenza diagnosis. The rest of the observation period was defined as the non-exposure period.	**Primary outcome:** Risk of stroke or MI	**MI** Median age was approximately 72 years, 59% were men, mean duration of observation was 5.6 years. The risk of MI was increased significantly from 1-28 days following influenza. 1-3 days: IR=4.95, 95% CI 4.43-5.53 4-7 days: IR=3.20, 95% CI 2.84–3.60 8-14 days: IR= 2.81, 95% CI 2.54–3.09 15-28 days: IR=1.95, 95% CI 1.79-2.12 29-90 days: IR=1.40, 95% CI 1.33-1.48 **Stroke** Median age was approximately 78.3 years, 44% were men, mean duration of observation was 5.3 years. The risk of stroke was increased significantly from 1-90 days following influenza. 1-3 days: IR=3.19, 95% CI 2.81-3.62 4-7 days: IR=2.34, 95% CI 2.05-2.66 8-14 days: IR= 2.09, 95% CI 1.89-2.32 15-28 days: IR=1.68, 95% CI 1.54-1.82 29-90 days: IR=1.33, 95% CI 1.26-1.40

Reduced the Risk of Cardiovascular Outcomes following Influenza Vaccination

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Tsivgoulis et al. 2018 **Greece/USA** **Systematic review & meta-analysis**	Risk of bias in RCTs was considered low	12 studies (7 prospective observational studies and 5 RCTs, n=543,311). Participants in 5 studies had a previous stroke (3.4%, 4.5%, 4.7%, 7.2% and 100%). Mean ages ranged from 58.4 to ≥75 years.	Studies compared the risk of cerebral ischemic events in patients receiving influenza (n=8) and/or pneumococcal vaccination (n=4) vs. controls.	**Primary outcomes:** Ischemic stroke, myocardial ischemic events and cardiovascular deaths	Mean duration of follow-up ranged from 6 months to 5.3 years. Overall, vaccination was not associated with a lower risk for ischemic stroke (RR=1.06, 95%CI 0.74–1.51, p= 0.77). In subgroup analysis restricted to influenza vaccine, the risk of ischemic stroke was reduced significantly (RR=0.87, 95% CI 0.79-0.96, p=0.004). Influenza vaccination was not associated with a significantly reduced risk of MI (RR=0.94, 95%CI: 0.73–1.22, p = 0.66) or cardiovascular mortality (RR =0.89, 95%CI: 0.41–1.91, p = 0.77).
Lee et al. 2017 **Korea** **Systematic review & meta-analysis**	Risk of bias was assessed as low in 7 studies	11 case-control or prospective studies including individuals ≥18 years (n=4), ≥60 years (n=1), ≥65 years (n=4) and age was not reported in 2 studies. In one study, all participants had diabetes, while another study included patients with recent ischemic stroke or TIA.	Examination of the association between influenza vaccination and stroke risk. Vaccination status was confirmed (n=7) or through recall (n=4). Most studies adjusted for lifestyle factors and/or smoking use of healthcare, non-seasonal data)	**Primary outcome:** Any stroke	Any stroke was the outcome of interest in 5 studies, first stroke in 3 studies, and recurrent stroke in one study. Stoke sub types (ischemic hemorrhagic) were assessed in 2 studies. Overall, the risk of stroke was reduced significantly in vaccinated persons (OR= 0.82; 95% CI 0.75–0.91; p < 0.001). The risk of stroke was significantly reduced in vaccinated in individuals in subgroup analyses of study quality, risk of bias, and stroke sub type. The risk was not reduced significantly in studies where vaccination status was established through recall.
Vamos et al. 2016	NA	124,503 persons ≥18 years with type 2 diabetes included in the	The association between hospitalizations for cardiovascular events and influenza vaccine was	**Primary outcome:** Hospital admissions for MI, stroke, heart failure	Over the study period 63.1% and 69% of persons were vaccinated. Vaccine recipients were older and generally more ill, had more

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UK **Retrospective study**		Clinical Practice Research Datalink from 2003-2009	examined. Cohorts were categorized into 4 periods: preinfluenza (Sept 1-start of flu season), influenza season, postinfluenza (end of flu season-April 1) and summer (May1-Aug 31).	and all-cause mortality	coexisting conditions and a larger number of medications prescribed. There were 5,142 hospital admissions for acute MI, 4,515 admissions for stroke, 14,154 admissions for pneumonia or influenza, 12,915 admissions for heart failure and 21,070 deaths. In fully-adjusted models, the risk of hospitalizations for MI was significant reduced for vaccinated persons during the flu season (IRR=0.78, 95% CI 0.65-0.93, p<001), but not for any of the other 3 periods. In fully-adjusted models, the risk of hospitalizations for stroke was significant reduced for vaccinated persons during the pre and post influenza seasons (IRR=0.74. 95% CI 0.65-0.85, p<0.001 and IRR=0.73, 95% CI 0.0.59-0.89, p<0.01, respectively) with a borderline reduction during influenza season (IRR=0.78, 95% CI 0.65-0.93, p<001), and a borderline significantly increased risk during the summer (IRR=1.17, 95% CI 1.00-1.41). In fully-adjusted models, the risk of hospitalizations for heart failure was significant reduced for vaccinated persons during all 3 periods, except summer. The risk of all-cause mortality was significantly reduced in all 4 periods. After further adjustment for residual confounding, vaccination was associated with a 19% reduction in the rate of hospital admissions for acute MI (IRR=0.81, 95% CI 0.62-1.04), 30% for stroke (IRR= 0.70, 95% CI 0.53-0.91), 22% for heart failure (IRR= 0.78, 95% CI 0.65-0.92) and 15% for pneumonia or influenza (IRR= 0.85, 95% CI 0.74-0.99) during influenza season

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Clar et al. 2015 **USA** **Cochrane Review**	1 trial rated as having low risk of bias, 5 trials rated as having moderate risk of bias	8 RCTs (n=12,029) including participants ≥18 years who received an influenza vaccination for routine influenza prevention. Persons with and without a history of cardiovascular disease (CVD) were included.	Trials compared influenza vaccination with placebo or no intervention. Follow-up ranged from 42 days to one year following vaccination. Six RCTs gave single injections of influenza vaccine, and 2 RCTs gave a second dose after 21 days. In 4 trials, influenza prevention was the primary outcome, while secondary prevention in persons with established coronary heart disease was the focus of the other trials.	**Primary outcomes:** MI, unstable angina and death from CVD, analyzed separately for persons with and without a history of CVD.	Study participants fell within 3 main groups. Group one (2 RCTs) included healthy adults ≥18 years. Group 2 (2 RCTs) included participants ≥ 60 years with controlled chronic conditions. Group 3 (4 RCTs) included participants with known coronary artery disease. Among the 4 secondary prevention trials, the risk of CVD death was reduced significantly among persons in the vaccine group (RR=0.44, 95% CI 0.26-0.76, p=0.003). In 3 trials reporting CV mortality as part of their safety analyses, there were no significant differences between groups.
Lavallée et al. 2014 **France** **Pooled analysis**	NA	Participants from 2 prospective cohort studies OPTIC (n=3,635) and the AMISTAD study (n=5,618) and one RCT (PERFORM trial, n=19,120). Participants in all studies had a recent, minor ischemic stroke or TIA.	Data from the 3 studies were pooled to examine the association between influenza vaccine and stroke risk. Data were analyzed using propensity score–adjustment approaches to minimize confounding bias. Prior to matching, there were significant baseline differences between groups (vaccinated vs. unvaccinated).	**Primary outcome:** A composite of nonfatal MI, nonfatal stroke, or vascular death up to 2 years. **Secondary outcomes:** Fata/ nonfatal MI and stroke	Following propensity matching, there were 5,054 vaccinated patients (88% of vaccinated patients) and 5,054 unvaccinated patients, with no significant differences in baseline characteristics. The risk of the primary outcome was not reduced significantly in vaccinated persons (HR= 0.97, 95% CI 0.85–1.11; p=0.67), nor were the risks of fata/nonfatal MI or stroke (HR= 0.84, 95% CI 0.59–1.18, p=0.30 and HR=1.01, 95% CI 0.88–1.17, p=0.89, respectively). The results were similar using a propensity score–adjusted model including the entire study cohort. There were no interactions found for age (≤75 or > 75 years), sex, stroke or TIA, or history of CAD (+/-) for the primary or secondary outcomes.
Siriwardena et al. 2014	NA	26,784 cases of stroke and 20,227 cases of TIA with equal numbers of	Associations between influenza and pneumococcal vaccines and stroke and TIA were examined. Models	**Primary outcome:** Stroke and TIA	Influenza vaccination given within the same season as the index date was associated with a significant reduction in the risk of stroke (adj

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UK **Case-control study**		matched controls included in the Clinical Practice Research Datalink from 2001-2009. 77% of participants were ≥65 years.	were adjusted for chronic heart disease, asthma/COPD, diabetes, chronic renal failure, chronic liver disease, splenectomy, immunosuppression/HIV, Charlson Index, hypertension, peripheral vascular disease, hyperlipidemia, smoking status, family history of stroke/TIA, family history of AMI, aspirin uptake, antihypertensive treatment, statin uptake, number of home visits and general practice consultations.		OR=0.76, 95%CI 0.72 to 0.80). Stroke risk was significantly lower with early vaccination (September to mid-November: OR= 0.74, 95% CI 0.70 to 0.78) but not later influenza vaccination (mid Nov-Feb). Influenza vaccination given within the same season as the index date was not associated with a significant reduction in the risk of TIA (adj OR=1.03, 95% CI 0.98 to 1.09). Pneumococcal vaccine given within the same season as the index date was not associated with a significant reduction in the risk of stroke or TIA.
Udell et al. 2013 **Canada** **Systematic review & meta-analysis**	5 trials were assessed as high quality	6 RCTs, 5 published, 1 unpublished (n= 6,735) including participants at high risk of cardiovascular disease. Mean age was 67 years. 51.3% women, 36.2% with a cardiac history.	Trials compared the outcomes of persons who received influenza vaccine (n=3,238) vs. placebo or control (n=3,231).	**Primary outcome:** A composite of major adverse cardiovascular events, including cardiovascular death or hospitalization for MI, unstable angina, stroke, heart failure, or urgent coronary revascularization **Secondary outcomes:** Cardiovascular mortality and other individual components of the primary outcome	Mean duration of follow-up was 7.9 months. Significantly fewer persons in the vaccinated group developed the primary outcome (2.9% vs. 4.7%; RR=0.65, 95% CI 0.48-0.86, p=.003). The absolute risk difference was 1.74% (95% CI, 0.81%-2.67%; p= .003) with an NNT of 58 (95% CI, 38-124) to prevent 1 major adverse cardiovascular event. There was a treatment interaction (p=0.02) whereby persons with an acute coronary syndrome benefitted more from active vaccination than persons with stable CAD. The risk of cardiovascular mortality was not reduced with active vaccination (1.3% vs. 1.7%, RR=0.81, 95% CI 0.36-1.83, p=0.61). The risk of fatal or nonfatal stroke was not reduced significantly with active vaccination (RR=0.66, 95% CI 0.30-1.47, p=0.31. Results from 2 trials included).
Vila-Corcoles	NA	27,204 individuals ≥60	The association between 23- valent	**Primary outcomes:**	Duration of follow-up was 12 months (26,444

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et al. 2012, 2014 **EPIVAC Study Group** **Spain** **Prospective study** ***CAPAMIS***		years assigned to 9 primary care centers in the Health Region of Tarragona, recruited on December 1, 2008. Mean age was 71.7 years, 44.6% were men.	polysaccharide pneumococcal vaccine (PPV23) and outcomes of interest was examined. Persons were classified as vaccinated if they had received at least one dose of PPV23 in the last 60 months before study start. Models were adjusted for a variety of stroke risk factors, in addition to age, sex, and the number of outpatient visits to family physician in 12-months before study start	Hospitalization for community acquired pneumonia (CAP), acute MI, ischaemic stroke and death from any cause	person-years). 34% of the cohort had been vaccinated. There were 121 cases of ischemic stroke (4.6, 95% CI 3.8-5.5, per 1,000 person-years). There were 30 strokes in 8,835 vaccinated person-years (3.4 per 1,000 person-years) compared with 91 strokes in 17,559 unvaccinated person-years (5.2 per 1,000 person-years). Vaccination significantly reduced the risk of ischaemic stroke (adjusted HR: 0.65; 95% CI 0.42-0.99; p = 0.048). The number needed to vaccinate to prevent one ischemic stroke was 560 (95% CI 295 to 5,649) The risks of all other outcomes were not reduced significantly following vaccination. **2014 (3-year outcomes)** There were 343 confirmed cases of ischemic stroke (incidence rate of 4.53 [95% CI: 4.08-5.04] cases per 1,000 person-years. Among these cases, 45 persons died in the first 30 days after diagnosis (mortality rate 13.1%, 95% CI: 9.7-17.2). In the multivariable models, vaccination did not reduce the risks of ischemic stroke, death from ischemic stroke or all-cause mortality
Smeeth et al. 2004 **UK** **Within-person case series**	NA	20,486 persons ≥18 years, with first-ever MI and 19,063 persons with a first-ever stroke who received influenza vaccine, included in the United Kingdom General Practice Research Database (GPRD) between 1987-2001.	The risk of stroke or MI among persons who received a single influenza vaccination within the vaccination season (September 1 to March 31), was examined. The incidence of MI and stroke during the exposure period was compared with the non-exposure period. The risk interval was defined	**Primary outcome:** Risk of stroke or MI	**MI** Median age was approximately 72 years, 59% were men, mean duration of observation was 5.6 years. The risk of MI was reduced significantly from 1-28 days following influenza vaccine. 1-3 days: IR=0.75, 95% CI 0.60–0.94 4-7 days: IR=0.68, 95% CI 0.56–0.84 8-14 days: IR= 0.73, 95% CI 0.63–0.85

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			as the 90-day period after influenza diagnosis. The rest of the observation period was defined as the non-exposure period.		15-28 days: IR=0.87, 95% CI 0.79–0.96 **Stroke** Median age was approximately 78.3 years, 44% were men, mean duration of observation was 5.3 years. The risk of stroke was reduced significantly from 1-28 days following influenza vaccine . 1-3 days: IR=0.77, 95% CI 0.61–0.97 4-7 days: IR=0.72, 95% CI 0.59–0.88 8-14 days: IR= 0.84, 95% CI 0.73–0.96 15-28 days: IR=0.88, 95% CI 0.80–0.97
Nichol et al. 2003 **USA** **Retrospective study**	NA	Persons ≥65 years, from 3 managed health care organizations living in the community (not in institutions) included in a 2-year interval. There were 140,055 participants in the 1998–1999 cohort and 146,328 in the 1999–2000 cohort	Data on stroke, influenza vaccination status and influenza were obtained from administrative databases, in addition to other data (demographics, comorbidities). Models were developed to examine the outcomes of vaccinated vs unvaccinated persons during the influenza season,	**Primary outcomes:** Hospitalization for cerebrovascular and cardiovascular disease and influenza	55.5% of the 1998/99 cohort and 59.7% of the 1999/2000 cohort received the influenza vaccine. **1998-1999 cohort** There were 1,677 (2.2%) and 1,888 (3.0%) hospitalizations for any of the study outcomes and 943 (1.2%) and 1361 (2.2%) deaths among vaccinated and unvaccinated participants, respectively. Persons who were vaccinated were significantly less likely to be hospitalized for: Influenza or pneumonia OR=0.68, 95% CI 0.60–0.78, NNT 347 Cardiac disease: OR=0.81, 95% CI 0.73–0.89, NNT 329 Cerebrovascular disease: OR=0.84, 95% CI 0.72–0.97, NNT 893 Any study outcome: OR=0.77, 95% CI 0.71–0.82, NNT 145 Hospitalization or death: OR=0.65, 95% CI 0.62–0.70, NNT 61 The pattern was similar for the 1999-2000 cohort. Influenza vaccination as not associated with

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					significant reductions in the odds of hospitalization during the summer months.

Association between Childhood Vaccines and Stroke

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
MacDonald et al. 2018 **Canada** **Retrospective study**	NA	Children born between January 1, 2006 and December 31, 2013, who were vaccinated between 11 and 23 months of age	Using administrative linked databases, the risk of ischemic stroke during the 12 months following vaccination for varicella (n= 325,729) was compared to nonvaccinated children (n= 43,263)	**Primary outcome:** Risk of ischemic stroke	The rate of ischemic stroke was 7.8 (95% CI 4.8– 10.9) per 100,000 person years at risk in the vaccination group and 6.8 (95% CI 1.3–12.2) for children in the non-vaccination group. After controlling for other stroke risk factors, including Moya Moya disease, Sickle cell disease, congenital heart disease, meningitis, severe sepsis, intracranial injury, varicella infection and stroke before the age of 11 months, the risk of ischemic stroke was not significantly higher in vaccinated children (HR= 1.6, 95% CI 0.7–3.7) in the 12 months following vaccination or during the 30 days following vaccination (HR=1.7, 95% CI 0.5–4.9).
Fullerton et al. 2015 **USA** **Case-control study** ***Vascular Effects of***	NA	355 children with acute ischemic stroke and 354 controls (234 routine visit and 120 trauma visit), recruited between January 2010 and March 2014, from 37 centers in 9 countries. Median age was 7.6 years (cases)	Models were developed to identify independent predictors of acute ischemic stroke. Exposures were determined through chart review and parental interviews. The model was adjusted for sex, season at enrollment, income level and age	**Primary outcome:** Ischemic stroke risk factors	A higher percentage of controls had received childhood vaccines (MMR, polio, diphtheria/pertussis/tetanus, varicella and Meningococcus) Independent predictors of ischemic stroke included infection in the previous week (OR= 6.3, 95% CI 3.2–12), poor vaccination status, as indicated by a composite variable capturing

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Infection in Pediatric Stroke (VIPS)		and 9.3 years (controls), 56.1% were boys (cases), and 55.1% (controls).			some/few/none routine vaccinations (OR=8.2, 95% CI 2.5-26), rural residence (OR=3.0, 95% CI 1.8–4.8) and black race (OR=2.0, 95% CI 1.1–3.7). The authors concluded that routine vaccinations may protect against stroke, by reducing the risk of infections.
Daley et al. 2014 **USA** **Prospective surveillance study**	NA	201,116 children, included in the Vaccine Safety Datalink, aged 4-6 years who received a combined diphtheria, tetanus, and acellular pertussis (DTaP) vaccine, with inactivated poliovirus (IPV) vaccine DTaP–IPV vaccine between January 4, 2009 and May 26, 2012. Median age at first vaccination was 53 months.	The number of adverse events observed following vaccination during the post vaccination risk window was compared to the number expected based on data from historical comparison groups, of children the same ages.	**Primary outcomes:** Meningitis/encephalitis; seizures; stroke; Guillain–Barré syndrome; Stevens–Johnson syndrome; anaphylaxis; serious allergic reactions other than anaphylaxis; and serious local reactions	The post vaccination risk window for stroke was determined to be 0-42 days. 97% of children received additional vaccines the same day (Measles–mumps–rubella and varicella). There was a single case of stroke during the risk period, compared with the expected number of 2.25 (RR=0.44), The risk of stroke was not significantly increased during the risk period. The risks of all other outcomes were not significantly increased during their respective risk periods, which ranged from 1-2 days to 0-42 days.
Donahue et al. 2008 **USA** **Retrospective study**	NA	3.25 million children, aged 11 months to 17 years, recruited from 8 medical care organizations included in the Vaccine Safety DataLink from January 1, 1991, to December 31, 2004. Mean age of vaccinated children was 1.9 years, and 7.9 years for those unvaccinated. 50% were boys.	The association between varicella vaccination and ischemic stroke and encephalitis during the following 12 months was assessed by comparing the outcomes of children who received varicella vaccination (n=1,142,920; 35.3%) and those who did not (2,097,553; 64.7%). The models were adjusted for calendar time, gender, and stroke risk factors	**Primary outcome:** Ischemic stroke, encephalitis	There were 203 new inpatient ischemic stroke diagnoses, of which 39 occurred in vaccinated children. Of those, 8 occurred within 12 months after vaccination. 164 unvaccinated children had a stroke. The proportion of children with ≥1 risk factor for stroke was 1.2% in the vaccinated group and 1.4% in the unvaccinated group. The risk was highest among children with Sickle cell disease (HR=170.4, 95% CI 97.0–299.3) and Systemic lupus erythematosus (HR=47.8, 95% CI 21.9–104.4). Among vaccinated children the risk of stroke was not significantly increased at any time

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					period during the 12 months after vaccination (0 to <1 months, 1 to <3 months, 3 to -<6 months, 6 to <9 months, 9 to <12 months).

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