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Literature Review: Influenza Immunization for Adult and Pediatric Patients Undergoing Cancer Treatment

Provincial Tumour Teams

Cancer Care Alberta

Literature Review SUPP-002
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Table 1: Summary of 2024 Clinical Practice Guidelines/Consensus Statements re. Vaccination for Seasonal Influenza in Cancer Patients, Aug. 2023 – Sep. 2024

Author, Year	Document Type	Patient Population	Recommendations
NCCN, 2024[1]	clinical practice guideline	adult patients w cancer	General Recommendations for Vaccination in Patients w Cancer: • Live vaccines should not be administered during chemo or periods of significant immunosuppression, such as treatment of GVHD • All household members should be up to date with vaccines • Patients w hematologic or solid tumour malignancies should receive inactivated or recombinant influenza vaccine annually Recommended Vaccination Schedule after Autologous or Allogeneic HCT: • Recommended timing of influenza (injectable) after HCT is 6 months; 1 dose, annually • Emerging therapies such as CAR-T appear to behave similar to patients who have undergone allogeneic transplant in terms of vaccine boosting recommendations
Pedrazzoli, 2023[2]	position paper	patients w solid tumours	Recommendations of Associazione Italiana di Oncologia Medica (AIOM): • Seasonal flu vaccination in patients w cancer safe, minimally invasive, and inexpensive • Seasonal influenza should be widely recommended in every patient w cancer who is candidate for oncological active therapy, irrespective of type of anticancer treatment (e.g., ICIs, chemo, targeted therapy) • Ideal time to administer vaccine in patients undergoing active treatment unclear. Preferably, vaccination should be scheduled before start of oncological therapies to avoid phase of leucopenia in case treatment has already begun. Recent papers have demonstrated efficacy and safety of vaccine also during active chemo • Seasonal flu, pneumococcal and SARS-CoV-2 can be co-administered • Quadrivalent or trivalent influenza vaccines recommended. Booster dose in same influenza season or high-dose vaccines may be used in elderly immunocompromised patients during chemo • Preferable to postpone any type of instrumental re-evaluation of oncological disease until 4 wks. after vaccination
Teh, 2023[3]	clinical practice guideline	patients w multiple myeloma (MM)	Recommendations of the Medical and Scientific Advisory Group Myeloma Australia and National Centre for Infections in Cancer: • Annual seasonal influenza vaccination recommended. Patients ≥65 yrs. should receive adjuvant IIV, whereas two IIV doses (1 mo. apart) could be considered based on national immunization program criteria (strong recommendation; level I evidence) • In first 2 mos. following autologous HCT, two doses of IIV recommended (strong recommendation; level I evidence)

Table 2: Summary of Peer-Reviewed Literature on Influenza Immunization in Adult Patients with Cancer, Jan. 2000 – Sep. 2024

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Gressens, 2024[4]	Prospective, single-centre cohort study ***(Level III)***	Patients with multiple myeloma; N=40 treated with daratumumab in the last 12 months	84	Two quadrivalent vaccine injections (Influvac Tetra, 15 µg HA for each strain) administered 28 ± 4 days apart 71 patients received both vaccine injections and had serum available at baseline and a month after each vaccine injection	• Seroprotection rates (titer ≥1/40) after the second vaccine injection were low across all vaccine subtypes (except for A-H3N2): 71.3% (A-H3N2), 19.7% (A-H1N1pdm09), 9.9% (B-Victoria), 11.3% (B-Yamagata). • Only A-H3N2 seroprotection rates significantly increased with the booster in daratumumab-treated pts (30% (12/40) after 1 injection vs 55% (22/40) after boost; p=0.01). • After propensity score weighting, daratumumab was not significantly associated with a reduced likelihood of seroprotection against at least one vaccine strain (OR 0.65; 95% CI 0.22-1.88). • Authors concluded that the overall low response rates in patients with multiple myeloma necessitates the development of alternative vaccination and prophylaxis strategies.

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Amdisen, 2024[5]	Retrospective cohort study ***(Level IV)***	All patients aged ≥18 years with an incident cancer diagnosis between 2022-2017	269,863	Not provided	• Influenza vaccination coverage = 14% for cancer pts <65 years and 51% for cancer pts ≥65 years. • No influenza vaccination in the previous season was associated with non-vaccination in the current season (<65 years: aPR = 2.75, 95 %CI = 2.71-2.80; ≥65 years: aPR = 5.15, 95 %CI = 5.10-5.21). • Hematological cancer pts receiving chemotherapy had lower vaccination prevalence compared with those not receiving chemotherapy.
Kinslow, 2024[6]	Retrospective cohort study ***(Level IV)***	Patients diagnosed with NSCLC between 2009-2015 identified using the SEER database	202,485	Not provided	• 53 of 1049 state-months (5.1%) had high flu activity. Monthly mortality rates during low and high flu months were 0.041 (95% CI 0.041–0.042) and 0.051 (95% CI 0.050–0.053), respectively (RR 1.24 [95% CI 1.21–1.27]). • Regional NSCLC mortality rates in the United States were higher during months with high influenzaactivity. This relationship was observed at the individual state-level and in all clinical and regional subgroups. • Median follow-up and survival times were 8 and 11 months, respectively, with N=141,651 deaths; pneumonia & influenza listed as the cause of death in 0.4% (N=592) of all death certificates. • Authors concluded that Increased regional influenza activity is associated with higher mortality rates for patients with NSCLC. Vaccine-directed initiatives and increased awareness amongst providers will be necessary to address the growing but potentially preventable burden of influenza-related lung cancer deaths.
Bersanelli, 2023[7]	prospective (INVIDIa-2 study) ***(Level III)***	Patients w advanced solid tumours receiving therapy w ICIs (alone or in combinations)	1188	See original study details Bersanelli 2021	• Original study population consisted of 1188 evaluable patients • After propensity score matching, 1004 patients considered (502 vaccinated and 502 unvaccinated), and 986 evaluable for OS • At median F/U of 20 mos., influenza vaccination demonstrated favourable impact on outcome receiving ICI in terms of median OS [27.0 mos. (CI 19.5–34.6) in vaccinated vs 20.9 mos. (16.6–25.2) in unvaccinated, p=0.003], median PFS [12.5 mos. (CI 10.4–14.6) vs 9.6 mos. (CI 7.9–11.4), p=0.049], and disease-control rate (74.7% vs 66.5%, p=0.005) • Multivariable analyses confirmed favourable impact of influenza vaccination in terms of OS (HR 0.75, 95% C.I. 0.62–0.92; p=0.005) and disease-control rate (OR 1.47, 95% C.I. 1.11–1.96; p=0.007). • Results suggest favourable immunological impact of influenza vaccination on outcome of cancer patients receiving ICI immunotherapy, further encouraging vaccine recommendation in this population and supporting translational investigations about possible synergy b/n antiviral and antitumour immunity
Jeong, 2023[8]	Retrospective ***(Level IV)***	cancer patients in Korea who received influenza vaccines during 2016/2017 and 2017/2018 seasons and who were aged ≥65 yrs.	431,276	Not provided	• Included all outcomes occurring on 1–84 days post-vaccination and evaluated all temporal risk windows, which started 1–28 days and ended 2–42 days • Used hierarchy of ICD-10 to identify statistically significant clustering. Study included 431,276 doses of flu vaccine

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		on date of influenza vaccination			• Only detected 1 signal of potential AE: other dorsopathies on 1–15 days (attributable risk 16.5 per 100,000, p=0.017); dorsopathy known AE of influenza vaccine • No statistically significant clusters found when analyzed by flu season • Findings provide reassurance of safety of influenza vaccine in elderly cancer patient population
Kodde, 2023[9]	retrospective ***(Level IV)***	patients w any kind of cancer; comparing outcome of hospitalized patients w cancer infected by SARS-CoV-2 or seasonal influenza	360	Not provided	• 29,284 patients w COVID-19 and 7442 patients w seasonal influenza included • Of these, 360 patients w seasonal influenza and 1625 patients w COVID-19 had any kind of cancer • Cancer patients w COVID-19 more likely to be admitted to ICU than cancer patients w seasonal influenza (29.4% vs 24.7%; OR 1.31, 95% CI 1.00–1.73 p<0.05) • No statistical significance observed in mechanical ventilation rate for cancer patients w COVID-19 vs those w seasonal influenza (17.2% vs 13.6% OR 1.34, 95% CI 0.96–1.86 p=0.09) • 34.9% of cancer patients w COVID-19 and 17.9% w seasonal influenza died (OR 2.45, 95% CI 1.81–3.32 p<0.01) • Risk factors among cancer patients w COVID-19 or seasonal influenza for in-hospital mortality included male gender, age, higher Elixhauser comorbidity index and metastatic cancer • Findings underline need of protective measurements to prevent infection w either COVID-19 or seasonal influenza, esp. in this high-risk population
Thompson, 2023[10]	retrospective ***(Level IV)***	patients w MM looking at influenza (FV) and pneumococcal (PV) vaccination rates and outcomes	2500	Not provided	• Of 4307 patients enrolled, 2543 and 2500 had study-entry data on influenza (FV) and pneumococcal vaccination (PV) status • Overall vaccination rates low (FV 39.6%, PV 30.2%) and varied by region • On separate multivariable analyses of OS by Cox model, FV in prior 2 yrs. and PV in prior 5 yrs. impacted OS (vs no vaccination; FV: HR, 0.73; 95% CI, 0.60-0.90; P=0.003; PV: HR, 0.51; 95% CI, 0.42-0.63; P< 0.0001) when adjusted for age, region, performance status, disease stage, cytogenetics at diagnosis, MM symptoms, disease status, time since diagnosis, and prior transplant • Proportions of deaths due to infections lower among vaccinated vs non-vaccinated patients (FV: 9.8% vs 15.3%, P = 0.142; PV: 9.9% vs 18.0%, P=0.032) • Patients w FV had generally lower health resource utilization vs patients w/o FV; patients w PV had higher or similar health resource utilization vs patients w/o PV • Vaccination important in MM and should be encouraged
Wei, 2023[11]	population-based retrospective self-controlled case series ***(Level V)***	Patients diagnosed w herpes zoster (HZ) w/n 6 mos. before and after receiving influenza vaccine in 2016; examining whether HZ risk increased after	1674	Publicly funded influenza vaccine used in Taiwan is trivalent vaccine containing 3 inactivated viruses: A H1N1, A H3N2, and influenza B. Viral strains for 2016–2017 Northern Hemisphere influenza vaccine were A/California/7/2009 (H1N1)-like virus, A/Hong Kong/4801/2014 (H3N2)-	• 13,728 patients diagnosed w HZ before and after receiving the influenza vaccine; 1,674 of these patients had cancer (12.2%) • IRR for days 1-15 significantly higher (IRR=1.11; 95% CI, 1.02-1.20), but insignificant for days 1-30 (IRR=1.04; 95% CI, 0.98-1.10) • In subgroup analysis, IRRs significantly higher in participants, including 50-64 yrs. old (1.16; 95% CI, 1.02-1.33), males (1.14;

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		receipt of influenza vaccine		like virus, and B/Brisbane/60/2008-like virus (Victoria lineage)	95% CI, 1.01-1.28), and healthier individuals (i.e., no history of cancer or autoimmune diseases)
Herati, 2022[12]	prospective cohort study ***(Level III)***	Cohort 1: adults w renal cell or urothelial carcinoma receiving immunotherapy and due to receive seasonal inactivated influenza vaccine. 2 groups: non-anti-PD-1 (aPD1)-based therapy (n=10) or aPD1-based therapy (n=29) Cohort 2: independently generated cohort at different institution. Adults w melanoma receiving immunotherapy (n=30) and healthy adults not receiving immunotherapy (n=27)	96	Participants received influenza vaccination on same day as one of their maintenance immunotherapy infusions (median of cycle 12 of aPD1 for Cohort 1 and cycle 7 for Cohort 2)	• Following influenza vaccination, subset of adults receiving aPD1 had more robust circulating Tfh (cTfh) responses than adults not receiving immunotherapy, and cTfh responses correlated w plasmablasts • PD-1 pathway blockade resulted in transcriptional signatures of increased cellular proliferation in cTfh and responding B cells compared to controls • aPD1 therapy associated w higher seroconversion rate after immunization, although some differences in antibody glycosylation and affinity evident at baseline • Subset of participants w robust changes in cTfh enriched for previous (or future) (irAEs) associated w immunotherapy • Latter observations suggest underlying change in Tfh-B cell and germinal center axis in subset of immunotherapy patients that may predispose to autoreactivity and also highlight analytical vaccination as approach that may reveal underlying immune predisposition to AEs • Results demonstrate dynamic effects of aPD1 therapy on influenza vaccine responses and provide framework for dissecting impact of immune modulating therapies on overall immune health
Lopez-Olivo, 2022[13]	systematic review/ meta-analysis ***(Level I)***	Cancer patients w solid tumours receiving ICIs	4705	Vaccine admin timing varied; 6 studies did not report details. In 2 uncontrolled trials, vaccine administered on first ICI dose on day 1, while in remaining studies, vaccination occurred during ICI therapy, or 7 days to 6 mos. before starting ICI therapy Half of studies reported use of trivalent (two type A viruses, H1N1 and H3N2, and one type B virus, B/Brisbane) or quadrivalent inactivated virus vaccine (two type A viruses, H1N1 and H3N2, and two type B viruses, B/Brisbane, and B/Phuker)	• 19 studies (26 publications, n=4705) included (89.5% observational) • Vaccinated patients (n=2108) reported lower rates of irAEs vs unvaccinated patients (32% vs 41%, respectively) • Seroprotection for influenza type A was 78%-79% and type B was 75% • Influenza and irAE-related death rates similar b/n groups • Pooled proportion of participants reporting lab-confirmed infection 2% (95% CI 0% to 6%), and influenza-like illness 14% (95% CI 2% to 32%) • No differences reported on rates of lab-confirmed infection b/n vaccinated and unvaccinated patients • Longer PFS and OS observed in vaccinated vs unvaccinated patients • Evidence suggests influenza vaccination safe in patients receiving ICIs, does not increase risk of irAEs, and may improve survival
Tsiakos, 2022[14]	systematic review/ meta-analysis ***(Level I)***	Cancer patients receiving ICIs	See results	≥1 dose of influenza vaccine	• 25 studies included in systematic review; 9 of which included in meta-analysis • Meta-analysis of 3 studies (n=589, weighted age 64 yrs., men 61%, influenza vaccinated 32%) showed pooled OR for death in influenza vaccinated vs nonvaccinated patients at 1.25 [(95% CI:0.81-1.92), p=non-significant • Meta-analysis of 6 studies (n=1285, weighted age 60 yrs., men 59%, influenza vaccinated 48%) showed pooled OR for any immune-related AEs in influenza vaccinated vs nonvaccinated patients at 0.82 [95% CI: 0.63-1.08, p=non-significant

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					• Similar results observed in sensitivity analyses for serious immune-related AEs, as well as when only peer-reviewed studies included • Influenza vaccination appears to be safe and reasonable intervention for cancer patients receiving ICIs. Most data from retro observational studies. Randomized studies needed to provide high-quality evidence

Yen, 2022[15]	cross-sectional study incorporating self-controlled case series; study
	
	(Level V)
		Adults 65 years or older in Taiwan, incl. w cancer; investigating association b/n seasonal influenza vaccination and incidence of GBS	374	All influenza vaccines used in Taiwan from 2003 to 2017 denatured virus-based vaccines; did not divide different brands of influenza vaccines into categories	• Of 13 482 122 adults aged ≥65 yrs. who received influenza vaccination, 374 hospitalized for GBS; 33 individuals (8.8%) had cancer
					• Mean (SD) age of study population 75.0 (6.1) yrs.; 215 (57.5%) men and 159 (42.5%) women
					• Incidence rate ratio (IRRs) for GBS during days:
					  ○ 1 to 7 was 0.91 (95% CI, 0.52-1.58; p=0.74 in patients w/o cancer vs 0.71 (95% CI, 0.10-5.16; p=0.73 in patients w cancer
					  ○ 1 to 14 was 0.84 (95% CI, 0.55-1.28; p=0.42 in patients w/o cancer vs 1.15 (95% CI, 0.35-3.75; p=0.82 in patients w cancer
					  ○ 1 to 42 was 0.94 (95% CI, 0.74-1.21; p=0.65 in patients w/o cancer vs 0.68 (95% CI, 0.28-1.64; p=0.39 in patients w cancer
					• Findings suggest influenza vaccination did not increase risk of GBS among adults aged ≥65 yrs. in Taiwan regardless of postvaccination period or underlying characteristics.

Alimam, 2021[16]	Prospective ***(Level III)***	Patients w diagnosis of essential thrombocythemia, polycytaemia vera or myelofibrosis Total of 19 patients enrolled + 6 healthy donors	25	Inactivated influenza A vaccine (Split virion, inactivated) administered by intramuscular injection Samples collected pre-vaccination and at approx. 3-wks. and 3-mos. post-vaccination	• Pre-vaccination note significantly less naïve CD4 T-cells (p=0.01), and activated CD4 T-cells (p=0.02) in MPN patients compared to healthy donors • At 3 wks. post-vaccination, MPN patients demonstrated less memory cell clusters, including central memory CD4 (p=6.93 × 10^3) and CM CD8 (p=5.11 × 10^3), memory B (p=0.03, p=0.01, and p=0.05) and resting memory B-cells (p=0.05), compared to healthy donors • When compared to healthy donors at 3 wks. post-vaccination, note significantly lower subset of Tregs known as Treg B-cells[10] (p=0.01), including CD161+ Treg B subpopulations (p=9.32×$10^3$and p=3.73×10^3, respectively) in MPN patients, which are highly suppressive subpopulation of Tregs • 3 wks. post-vaccination MPN patients had significantly higher number of naïve CD4 T-cells compared to healthy donors (p=6.93 × 10^3), which may suggest delayed immune response • By 3 mos. post-vaccination significant reductions in memory B cells (p=0.04 and *P*=0.01) and CD161+ Treg B-cells (p=0.01 and p=0.01) still evident in MPN patients. Although to lesser extent, it had not reverted to pre-vaccination state • Compared to healthy donors, reductions in naïve CD4 T-cells (p=0.03) from pre-vaccination in MPN patients could also be

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					observed at 3 mos. post-vaccination, paralleled w increase in activated CD4 T-cells (p=0.03) • Did not observe significant effect of disease subtype, molecular status or cytoreductive therapy on vaccination responses • Data supports routine influenza A immunization in accordance w national recommendations; however, additional studies mandated to evaluate both effectiveness of vaccine responses and 'memory' in larger cohort of MPN patients to determine if alternative strategies for vaccination required
Atalla, 2021[17]	systematic review & meta-analysis ***(Level I)***	Patients of any age w lab-confirmed influenza w hematologic malignancies and HSCT	1787		• 52 studies w data on 1787 patients included • During seasonal epidemics, influenza-related in-hospital mortality 16.60% (95% CI, 7.49%–27.7%), w significantly higher death rate in adults compared to pediatric patients (19.55% [95% CI, 10.59%–29.97%] vs 0.96% [95% CI, 0%–6.77%]; *P* < 0.001) • Complications from influenza, such as LRTI, developed in 35.44% of patients w hematologic malignancies and HSCT recipients, w statistically significant difference b/n adults and children (46.14% vs 19.92%; p<0.001) • However, infection resulted in higher hospital admission rate in pediatric patients compared to adults (61.62% vs 22.48%; p 0.001) • For 2009 H1N1 pandemic, no statistically significant differences found b/n adult and pediatric patients when comparing rates of influenza-related in-hospital mortality, LRTI, and hospital admission • Similarly, no significant differences noted in any outcomes of interest when comparing H1N1 pandemic w seasonal epidemics
Aznab, 2021[18]	Prospective ***(Level III)***	Patients divided into 2 categories: hematologic cancer (including multiple myeloma, lymphoma, and Hodgkin's disease) and solid cancer (other than hematological)	288	One 0.5 ml dose of InfluVac TETRA 2020/2021 surface antigen/inactivate, Abbott Biological B.V, Netherlands Time for vaccination in those who received chemo q3wks was end of 3rd wk. and before start of new course of chemo, although new term postponed for 4 days. Same is true for 2-wk. treatments	• From 288 patients (median age: 52 yrs. (range 18-79), 112 (38.9%) males and 176 (61.1%) female) w different types of cancers, only 2 patients had adverse effect of vaccination (including bone pain, runny nose, and fatigue), and one had COVID-19 ten days after vaccination • Rest of patients did not show any side effects due to flu vaccination after 1 mo. of follow-up • Cancer patients recommended to receive flu vaccine annually
Bersanelli, 2021[19]	Prospective (INVIDIa-2 study) ***(Level III)***	Patients w advanced solid tumours receiving therapy w ICIs (alone or in combinations)	1188	Trivalent - adjuvanted, n=158 (27.2%) - non-adjuvanted, n=15 (2.6%) Quadrivalent - adjuvanted, n=0 - non-adjuvanted, n=346 (59.5%)	• Enrolled 1279 patients; 1188 patients evaluable for primary endpoint analysis • 48.9% (581/1188) received influenza vaccination • Overall influenza-like illness incidence = 8.2% (98 patients) • Vaccinated patients significantly more frequently elderly (p<0.0001), males (p=0.004), w poor ECOG performance status (p=0.009), affected by lung cancer (p=0.01), and by other non-cancer comorbidities (p<0.0001) when compared w unvaccinated • Influenza-like illness incidence not different based on influenza vaccination: time-to-influenza-like illness similar in vaccinated and unvaccinated patients (p=0.62)

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					• Influenza-like illness complications significantly less frequent for patients receiving vaccination (11.8% vs 38.3% in unvaccinated, p=0.002) • Influenza-like illness-related IV therapies significantly less frequent in vaccinated patients than in unvaccinated (11.8% vs 29.8%, p=0.027) • Influenza-like illness lethality, 0% in vaccinated and 4.3% in unvaccinated patients • Vaccine-related AEs rare and mild (1.5%, grades 1-2) • INVIDIa-2 study results support positive recommendation for influenza vaccination in patients w advanced cancer receiving immunotherapy
Desage, 2021[20]	systematic review ***(Level I)***	Inclusion criteria focused on immune-related AE occurrence in cancer patients treated by ICIs and being vaccinated. All publications related to live vaccine or cancer vaccine excluded		Request formulated in MEDLINE used “vaccination” [MeSH Terms] OR “influenza vaccine”)	• 5 studies and 5 abstracts selected. Review highlights lack of data. Most studies retrospective w few patients included • Most studies published in literature re. influenza vaccination: no study evaluated ICIs interactions and other inactivated vaccines • Studies analysis showed multiple confounding factors. Type of cancer, vaccines (trivalent vs quadrivalent), immunotherapies used (anti-PD-1, anti-PD-L1, anti-CTLA-4) different from one study to another • Timing of vaccine relative to start of checkpoint inhibition heterogeneous and unspecified in selected studies. Thus, retrospective nature of analyzed studies added to such confounding factors • Vaccination for patients undergoing ICI treatment seems to induce seroprotective humoral response and may raise immune-related AEs • Influenza vaccination for patients treated w ICIs not associated w treatment interruption due to progression or clinical deterioration • Inactivated vaccines not contraindicated in patients w ICI treatment, but larger prospective studies needed, especially w ICIs combination therapies
Gatti, 2021[21]	Retrospective ***(Level IV)***	Patients receiving ICIs	590	Any type of vaccine against influenza virus	• Over observed period, out of total of 712,776 AEs following immunization, 191 (0.03%) reports of myopericarditis mentioning influenza vaccine as suspect collected w/n VAERS • In VigiBase®, 246,864 reports mentioning influenza vaccine as suspect agent found, and myocarditis/pericarditis reported in 399 cases (0.16%) • No case of MP reporting concomitant use of ICIs and influenza vaccine found in VAERS, while 3 cases of myocarditis retrieved in VigiBase. All cases unclassifiable for causality assessment b/c of lack of data concerning latency. According to Drug-Interaction Probability Scale, 1 report categorized as possible and 2 as doubtful • Paucity of cases coupled w doubtful causality assessment make potential interaction b/n influenza vaccines and ICIs in cancer patients negligible from clinical and epidemiological standpoints • Findings support cardiovascular safety of influenza vaccination, which remains strongly recommended in cancer patients

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Gogenur, 2021[22]	register-based study ***(Level IV)***	Patients undergoing curative surgery for colorectal surgery: 1) who never received vaccine and 2) who received vaccine b/n 1 yr. before surgery and 6 mos. after surgery	9869	Trivalent inactivated influenza vaccines	• 9869 patients included. 5146 of whom received influenza vaccine • In multivariate Cox regression model, no association w risk of recurrence (HR 0.94, 95% CI 0.85–1.05), overall mortality (HR 0.95, 95% CI 0.87–1.03), and disease-free survival (HR 1.01, 95% CI 0.94–1.09) • In patients receiving vaccine b/n 6 and 12 mos. before surgery, association to decreased risk of recurrence identified (HR 0.78, 95% CI 0.67–0.91) but no association w overall mortality (HR 1.04, 95% CI 0.93–1.17) or disease-free survival (HR 0.97, 95% CI 0.88–1.07) • Contradictory results revealed in subgroup analysis of patients, but group number of subgroups had low numbers (i.e., power problem) • Study's findings support need for further clinical studies to investigate causal effects of influenza vaccine on oncological outcomes
Li, 2021[23]	Retrospective ***(Level IV)***	Patients aged ≥18 yrs. hospitalized w diagnosis of cancer	47850	Annual influenza vaccine b/n 2012-2014 (types not reported)	• Identified 13,186,849 weighted cancer-related hospitalizations during study period, and 47,850 of them (0.36%) had concomitant diagnosis of influenza • After propensity score matching, cancer patients w concomitant influenza had higher mortality (5.4% vs 4.2%; OR, 1.30; 95% CI, 1.13 to 1.49; p<0.001), longer length of stay (6.3 days vs 5.6 days; p<0.001) but lower costs (US$14 605.9 vs US$14 625.5; p<0.001) in hospital than those w/o influenza • In addition, cancer patients w influenza had higher incidence of complications, including pneumonia (18.4% vs 13.2%; OR, 1.49; 95% CI, 1.37 to 1.62; p<0.001), neutropenia (7.1% vs 3.4%; OR, 2.18; 95% CI, 1.91 to 2.50; p<0.001), sepsis (19.5% vs 9.3%; OR, 2.36; 95% CI, 2.16 to 2.58; p<0.001), dehydration (14.8% vs 8.8%; OR, 1.80; 95% CI, 1.65 to 1.97; p<0.001) and acute kidney injury (19.9% vs 17.6%; OR, 1.16; 95% CI, 1.08 to 1.25; p<0.001) than those w/o influenza • Older age, no insurance, more comorbidities, lung cancer and hematological malignancy independently associated w higher mortality • Influenza associated w worse in-hospital clinical outcomes among hospitalized patients w malignancy. Annual influenza vaccination and early initiation of antiviral therapy recommended
Spagnolo, 2021[24]	systematic review ***(Level I)***	Cancer patients receiving ICIs	1124	Several types of influenza vaccines reported	• 10 studies assessing safety and 8 assessing efficacy; total of 1124 and 986 vaccinated patients, respectively • Most patients had melanoma or lung cancer and received single agent anti-PD-1, but also other tumour types and immunotherapy combinations represented • No severe vaccination-related toxicities reported • Pooled incidence of any grade ICI-related AEs 28.9% • In 6 studies specifying incidence of grade 3-4 toxicities, pooled incidence 7.5% • No grade 5 toxicities reported

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					• No pooled descriptive analysis conducted in studies reporting efficacy outcomes due to heterogeneity of endpoints and data reporting Nevertheless, among 8 studies included, 7 reported positive efficacy outcomes of influenza vaccination • Results support safety and efficacy of influenza vaccination in cancer patients receiving ICIs
Teh, 2021[25]	randomized controlled trial ***(Level II)***	Patients attending outpatient clinics and those electively admitted for HCT. Aged ≥18 yrs. who w/n 12 mos following autoHCT Patients randomized 1:1 to high-dose (HD) inactivated influenza vaccination (IIV) followed by standard dose (SD) vaccine (HD-SD arm) or 2 SD vaccines (SD-SD arm) 4 wks. apart	68	Vaccines TIV HD (Fluzone-HD; Sanofi-Pasteur) and QIV SD (FluQuadri; Sanofi-Pasteur) containing following strains; A/Michigan/45/2015 (H1N1)pdm09–like virus, A/Switzerland/8060/2017 (H3N2)–like virus, B/Phuket/3073/2013-like virus (Yamagata lineage) for both formulations, and B/Colorado/06/2017-like virus (Victoria lineage) for QIV vaccine. HD vaccine contained 60 µg hemagglutinin per strain per 0.5 mL while SD vaccine contained 15 µg hemagglutinin per strain per 0.5 mL Timing of vaccination from HCT determined by timing of Southern Hemisphere influenza season and patients could be vaccinated if ≥4 wks. post-autoHCT	• 68 patients enrolled (34/arm) w median age 61.5 yrs., majority male (68%) w myeloma (68%) • Median time from autoHCT to vaccination 2.3 mos • For HD-SD and SD-SD arms, percentages of patients achieving seroprotection 75.8% and 79.4% for H1N1, 84.9% and 88.2% for H3N2 (all *P*>0.05), and 78.8% and 97.1% for influenza-B/Yamagata (*P*=0.03), respectively • Seroconversion rates, GMTs and GMT ratios, and number of influenza-like illness or laboratory-confirmed influenza not significantly different b/n arms • AE rates similar • Receipt of concurrent cancer therapy independently associated w higher odds of seroconversion (OR, 4.3; 95% CI, 1.2–14.9; p=0.02) • High seroprotection and seroconversion rates against all influenza strains can be achieved w vaccination as early as 2 mos. post-auto HCT w either 2-dose vaccine schedules
Valachis, 2021[26]	Retrospective ***(Level IV)***	All patients previously not treated w checkpoint inhibitors and who received monotherapy w PD-1 or PD-L1 blocker	303	Patients considered vaccinated if they had received influenza vaccination during treatment w checkpoint inhibitor or up to 60 days prior to treatment initiation (n=236)	• Most common type of malignancy melanoma (47.8%) followed by NSCL cancer (31.0%) • Statistically significant longer PFS and OS observed in multivariate analyses at 6-mo. landmark time in vaccinated compared to non-vaccinated group after adjustment for age, gender, comorbidity, performance status, CNS metastasis and line of treatment (***p*=**0.041 and 0.028, respectively) • Incidence of any irAE grade comparable b/n vaccinated and non-vaccinated group (UICC, cancer type CCI and psychiatric disease • 0.85) • Study indicates survival improves w influenza vaccination while not increasing risk for side effects in cancer patients treated w checkpoint inhibitors
Whitaker, 2021[27]	Prospective ***(Level III)***	Patients w monoclonal B-cell lymphocytosis (MBL) and previously untreated chronic lymphocytic leukemia (CLL)	30	2013-2014 and 2014-2015 high-dose trivalent influenza vaccine (HD IIV; Fluzone® High-Dose; Sanofi Pasteur)	• 17 CLL and 13 MBL patients included. Median age 69.5 yrs. • Day 28 seroprotection rates for cohort 19/30 (63.3%) for A/H1N1; 21/23 (91.3%) for A/H3N2; and 13/30 (43.3%) for influenza B • Those w MBL achieved higher day 28 hemagglutination inhibition geometric mean titers (54.1 [4.9, 600.1] vs 12.1 [1.3, 110.1]; p=0.01) and higher Day 28 seroprotection rates (76.9% vs 17.6%; p=0.002) against influenza B-vaccine strain virus than those w CLL • Immunogenicity of HD IIV3 in patients w CLL and MBL lower than reported in healthy adults. Immunogenicity to influenza B greater in those w MBL than CLL

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Ayoola, 2020[28]	prospective ***(Level III)***	Patients w non-haematological malignancy on active treatment (chemo and targeted therapy)	53	1 dose of 2011/2012 trivalent vaccine containing strains A/California/7/2009(H1N1), A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008 (Fluvax) prior to or in-between treatment cycles	• Seroconversion rate at 3 wks. 35%, 30% and 22.5% to H1N1, H3N2 and B/Bris strains, respectively. No new cases of late seroconversion at 6 wks. or 24 wks. • Seroconversion rate at 3 wks. 72.5%, 65% and 40%, respectively, to H1N1, H3N2 and B/Bris. Seroconversion rate at 24 wks. to H1N1, H3N2 and B/Bris 40%, 52.5% and 17.5%, respectively. • Patients on various solid tumour treatments achieve sero-protection rate congruent w general population. Sero-protection haemagglutination-inhibiting antibody titres not sustained at 24 wks. postvaccination
Bayle, 2020[29]	prospective ***(Level III)***	Advanced cancer patients receiving single-agent ICI targeting PD-1 NSCLC, n=25 Urothelial carcinoma, n=5 Males 83%, median age 63 yrs. (range: 47-78)] Nivolumab n=7, Pembrolizumab n=8) or PD-L1 (atezolizumab n=15)	30	Single, standard dose of French National Health authorities-approved, subcutaneous influenza vaccine 7 (±2) days after last administration of ICI	• Median time under ICI treatment at time of vaccination 3 mos. (range: 1-28) • Influenza A (H1N1 and H3N2) antibody titres measured at baseline and at days 21 and 42 after vaccination, according to WHO-approved assay • At day 42 post-vaccination, observed seroprotective rates of 71%, 63% and 67% against H1N1, and 57%, 63% and 67% against H3N2 in patients receiving nivolumab, pembrolizumab and atezolizumab, respectively • Seroconversion factors high, w 7 patients (23%) showing seroconversion factor >1000 • Influenza infection not documented among 30 vaccinated patients for 6 mos. following vaccination • No grade 4-5 irAE observed, and 15 patients (50%) developed grade 1-3 irAE for 6 mos. following influenza vaccination shot, proportion similar to that observed in patients receiving single-agent ICIs • Data suggest that influenza vaccination in patients under ICIs safe and effective
Bersanelli, 2020[30]	Retrospective ***(Level IV)***	Patients w primary advanced cancer and any systemic treatment w anti-programmed cell death receptor 1 (PD-1), anti-PD-1 ligand (PD-L1) or anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies during Italian influenza season 2016–2017 1. Vaccinated 2. Nonvaccinated	 79 221	Trivalent (two type A viruses, H1N1 and H3N2, and one type B virus, B/Brisbane) or quadrivalent (adding a type B virus, B/Phuket) inactivated virus vaccine	• Both at univariate and multivariate analysis, occurrence of influenza syndrome significantly related to better OS in overall population (OR: 0.53 [95% CI: 0.32–0.88]; p=0.01) • In lung cancer subgroup, receiving flu vaccine and/or developing influenza syndrome related to better OS (p=0.04) • W/n elderly patients, flu vaccine main variable for relative OS advantage (p=0.05) • Receiving flu vaccine and/or developing influenza syndrome related to better OS w/n INVIDIa population
Collins, 2020[31]	Retrospective ***(Level IV)***	Hospitalized immunocompromised adults w influenza	3633	Details re. vaccination type not reported; influenza season under study was 2011-2015	• Among 35 348 adults, 3633 (10%) IC; cancer (44%), nonsteroid immunosuppressive therapy (44%), and HIV (18%) most common • Immunocompromised patients more likely than non-immunocompromised patients to have received influenza

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					vaccination (53% vs 46%; *P*<0.001), and ~85% of both groups received antivirals • In multivariable analysis, immunocompromised adults had higher mortality (aOR, 1.46; 95% CI, 1.20-1.76) • Intensive care more likely among immunocompromised patients 65–79 yrs. (aOR, 1.25; 95% CI, 1.06-1.48) and those >80 yrs. (aOR, 1.35; 95% CI, 1.06-1.73) compared w non-immunocompromised patients in those age groups • Immunocompromised patients hospitalized longer (adjusted hazard ratio of discharge, 0.86; 95% CI, 0.83-0.88) and more likely to require mechanical ventilation (aOR, 1.19; 95% CI, 1.05-1.36) • In subgroup analyses comparing patients w listed condition w non-immunocompromised patients, mortality more likely in patients w cancer and patients receiving nonsteroid immunosuppressive therapy (aOR [95% CI], 1.71 [1.35-2.17] and 1.66 [1.29-2.15], respectively), less likely in solid organ transplant recipients (aOR, 0.36; 95% CI, 0.15-0.88), and not statistically different in patients w HIV/AIDS (aOR, 1.31; 95% CI, 0.75-2.28) • Substantial morbidity and mortality occurred among immunocompromised adults hospitalized w influenza
Failing, 2020[32]	retrospective ***(Level IV)***	Patients >18 yrs. who received ≥1 dose of pembrolizumab during any influenza season from Sept 2014 to Aug 2017 1. ≥1 influenza vaccination 2. Nonvaccinated	 70 92	W/n vaccination cohort, 9 patients (12.7%) received influenza vaccines in 2 flu seasons, 7 patients (10%) received influenza vaccines in 3 flu seasons 56.7% of vaccinated patients received high-dose (trivalent) vaccines, 35.8% received quadrivalent vaccines, and 7.5% received vaccines w unspecified type	• Vaccinated group significantly older (*P*=0.002) and received more cycles of pembrolizumab (*P*=0.006) • Incidence of any grade irAE in vaccinated group trended toward being lower (25.7% vs 40.2%; p=0.07) compared w nonvaccinated group • Influenza vaccination independently associated w fewer irAEs, w OR 0.4 (95% CI, 0.2 to 0.9; p=0.03) in multivariable analyses • Vaccinated group less likely to have irAE compared w nonvaccinated group (24.7% vs 34.4% at 12 mos.; p=0.05), w death as competing risk • Median irAE-free duration in vaccinated group longer than nonvaccinated group (not reached vs 28 mos.; p=0.037) • Influenza vaccination in patients w cancer receiving ICI therapy not associated w increased irAE
Gogenur, 2020[33]	Retrospective ***(Level IV)***	Patients undergoing curative surgery for solid tumors Categorized in 2 groups; patients who never received vaccine (n=18905) and patients who received vaccine w/n 6 mos after surgery but not w/n 1 yr. prior to surgery (n=2557), thus securing period of no exposure to vaccine prior to surgery	21462	Trivalent inactivated influenza vaccine	• In Cox regression model, decrease in overall mortality (HR=0.89, 95% CI=0.81-0.99, p=0.03) and cancer-related mortality (HR=0.82, 95% CI=0.71-0.93, p=0.003) found among patients given vaccine vs patients never receiving vaccine • In predefined subgroup of patients receiving vaccine w/n 30 days after surgery, decrease in overall mortality (HR=0.82, 95% CI=0.72-0.94, p=0.007) and cancer-specific mortality (HR=0.70, 95% CI=0.53-0.91, p=0.009) found • No association evident in patients receiving vaccine after 30 days to 6 mos. after surgery (overall mortality: HR=0.96, 95% CI=0.86-1.07, p=0.46); cancer-specific mortality: HR=0.88, 95% CI=0.76-1.03, p=0.12)

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		Vaccinated patients classified into 2 groups: patients receiving vaccine w/n 30 days postop (n=669) and patients receiving vaccine w/n 30 days to 6 mos. postop (n=1888)			• Found overall association b/n survival and having influenza vaccine after oncological surgery. Also found that when patients received influenza vaccine b/n 0 and 30 days after surgery, association w overall and cancer-related mortality, even when controlling for age, sex, UICC, cancer type CCI and psychiatric disease • Findings must be investigated in larger clinical trials where both immunological biomarkers and survival outcomes included
Joona, 2020[34]	prospective ***(Level III)***	1. Female patients >18 yrs. w stage I, II, or operable stage III HER2+ breast cancer treated w trastuzumab in adjuvant setting 2. Healthy controls	20 37	Trivalent influenza vaccine containing inactivated A/California/7/2009(H1N1) pdm09, A/Hongkong4801/2014(H3N2), and B/Brisbane/60/2008	• No difference in seroprotection rate between trastuzumab-treated patients and controls observed for either H1N1 (100% in both groups) or B strain (78.9% vs 89.2%, p =0.423) • Immunogenicity analysis for influenza B strain using repeated measures ANOVA showed significant differences among 3 time points in both trastuzumab-treated patients (baseline vs 4 wks., p value <0.001; baseline vs 12 wks., p value=0.042) and healthy controls (baseline vs 4 wks., p value <0.001; baseline vs 12 wks., p value=0.012) • Immunogenicity analysis for H1N1 strain showed significant differences among 3 time points in both trastuzumab-treated patients (baseline vs 4 wks., p value<0.001; baseline vs 12 wks., p value=0.039) and healthy controls (baseline vs 4 wks., p value<0.001; baseline vs 12 wks., p value=0.014) • AEs in trastuzumab-treated group uncommon and mild w only 1 serious AE not related to vaccination • Current data support recommendation to offer influenza vaccination in breast cancer patients treated w SC trastuzumab
Kang, 2020[35]	prospective ***(Level III)***	Patients w cancer receiving: 1. anti–PD-1 ICIs (Opdivo, Bristol-Myers Squibb; or Keytruda, Merck) 2. Cytotoxic CT	11 29	Quadrivalent influenza vaccine (GC Fluquadrivalent PFS [2018/2019], GC Pharma), which contained 15 µg purified viral antigen from strains A/Singapore/GP1908/2015 IVR-180 (H1N1), A/ Singapore/INFIMH-16–0019/2016 IVR-186 (H3N2), B/ Phuket/3073/2013 (Yamagata), and B/Maryland/15/2016 NYMC BX-69A (Victoria) Vaccine administered on day 1 of CT cycle	• When comparing ICI and cytotoxic CT groups, H1N1-specific IL-4 or IFN-γ–expressing CD4+ T cells, IL-2, IL-4, IFN-γ, or CD107a-expressing CD8+ T cells, H3N2-specific IFN-γ–expressing CD4+ T cells, and CD107aexpressing CD8+ T cells more frequent in ICI group • Fold changes in polyfunctional H3N2-specific CD4+ (median, 156.0 vs 95.7; P=0.005) and CD8+ (155.0 vs 103.4; P=0.044) T cells greater in ICI group • ICI administration strongly associated w adequate cell-mediated immunogenicity response for both CD4+ and CD8+ T cells (P=0.003) • Cell-mediated immunogenicity responses following influenza vaccination stronger in ICI group than in cytotoxic CT group • Influenza vaccination should be strongly recommended in patients w cancer receiving ICIs
Keam, 2020[36] *(*no access to supplementary data to report*	prospective ***(Level III)***	Patients >20 yrs. w cancer who received: 1. ICIs 2. Cytotoxic CT	47 92	Quadrivalent influenza vaccine (GCFLU Quadrivalent Pre-filled Syringe injection. [2018/2019]; GC Pharma). Each 0.5-mL dose contained 15 µg of purified viral antigen from strains: A/Singapore/GP1908/2015 IVR-180	• Most common cancer lung cancer in both groups. Nivolumab and pembrolizumab most used ICIs • Seroprotection and seroconversion rates significantly higher in ICI group than in cytotoxic CT group for all strains, except for H1N1 strain

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exact numbers in results section)				(H1N1), A/Singapore/ INFIMH-16–0019/2016 IVR-186 (H3N2), B/Phuket/3073/2013 (Yamagata), and B/Maryland/15/2016 NYMC BX-69A (Victoria) Vaccine administered concomitantly on day 1 of CT cycle	• Postvaccination geometric mean titers for hemagglutination inhibition antibodies significantly higher in ICI group for all strains, after adjusting for prevaccination geometric mean titers • Proportions of cumulative strains detected in seroprotection or seroconversion tests significantly higher in ICI than in cytotoxic CT group • Found independent association between ICI and number of strains protected against, after adjusting for age > 60 yrs., cancer type, and baseline hemagglutination inhibition antibody titers • In all subgroup analyses, ICI group showed tendency toward higher seroprotection rates than cytotoxic CT group • Among 47 and 92 patients in ICI and cytotoxic CT groups, respectively, rates of conventional AE comparable • Among patients receiving ICIs, identified 4 (9%) irAE during follow-up period, all grade 1 • Results support annual influenza vaccinations for cancer patients receiving ICIs
Bersanelli, 2019[37]	systematic review ***(Level I)***	Advanced cancer patients receiving ICIs	1993	Any study reporting or considering use of influenza vaccination during therapy w ICIs included	• Identified 9 studies (retrospective and prospective) • Currently no reliable data to support use of split vaccines during cancer immunotherapy; safety and efficacy of vaccine during ICI therapy not specifically proven • Only few retrospective studies currently available in literature on topic • Only based on pharmacological characteristics of ICI antibodies, influenza vaccination has been considered as potentially safe in patients treated w cancer immunotherapy • No prospective studies assessing clinical efficacy of influenza vaccination during immunotherapy w ICI in cancer patients • Scarce and controversial evidence about influenza vaccination during anticancer therapy w ICI confirms need of more robust data on safety of vaccine during immunotherapy and, consequently, on its advisability in apopulation where its usefulness not yet specifically been proven
Blanchette, 2019[38]	retrospective test-negative ***(Level IV)***	Adult patients w cancer and survivors ≥18 yrs. who underwent diagnostic testing for influenza during 2010-2011 to 2015-2016 influenza seasons in ON, Canada	26463	Not reported (vaccination status determined from physician and pharmacist billing claims)	• Identified 26,463 patients w cancer who underwent influenza testing, w 4,320 test-positive cases (16%) and 11,783 (45%) vaccinated • Mean age 70 yrs., 52% male, mean time since diagnosis 6 yrs., 69% had solid tumor malignancies, and 23% received active CT • Vaccine effectiveness against laboratory-confirmed influenza 21% (95% CI, 15% to 26%), and vaccine effectiveness against laboratory-confirmed influenza hospitalization 20% (95% CI, 13% to 26%) • For patients w solid tumor malignancies, vaccine effectiveness 25% (95% CI, 18% to 31%), compared w 8% (95% CI, –5% to 19%) for patients w hematologic malignancies (P=0.015)

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					• Active CT usage did not significantly affect vaccine effectiveness, especially among patients w solid tumor cancer • Results support recommendations for influenza vaccination for patients w cancer. Strategies to optimize influenza prevention among patients w cancer are warranted
Chong, 2019[39]	retrospective review ***(Level IV)***	Patients w solid tumours (lung=165, melanoma=71, other=134) treated w ICIs	370	2014-15, 2015-16, or 2016-17 inactivated trivalent (N=207) or quadrivalent (N=163) standard (N=199) or high dose (N=171) influenza vaccine w/n 65 days of cancer therapy	• N=75 (20%) experienced a new onset irAE (any grade): N=5 (7%) grade 1, N=40 (53%) grade 2, N=27 (36%) grade 3, N=3 (4%) grade 4; no grade 5 • Main types of irAEs: endocrine (28% of all AEs) pneumonitis (25%), colitis (13%), transaminitis (12%) • Proportion of patients who experienced any irAE highest among those treated w ipilimumab+nivolumab (25/82, 30%) • For patients on an anti-PD1 agent only, overall irAE rate 17% (38/227) • Proportion of patients who experienced serious (grade 3 or 4) irAEs higher among those treated w ipilimumab+nivolumab (11/82, 13%) vs those treated w anti-PD1 agents alone (15/227, 6.6%)

Gwynn, 2019[40]	prospective case series ***(Level V)***	Patients w solid tumours treated w ICIs	24	2017-18 inactivated quadrivalent influenza vaccine	• N=7 patients w immune mediated AEs (any grade) in 60 day follow up period (1 patient experienced 2)
					  ○ N=3 grade 1-2 rash
					  ○ N=1 grade 1-2 hypothyroidism
					  ○ N=1 grade 1-2 myalgia
					  ○ N=1 grade 1-2 colitis
					  ○ N=2 severe immune mediated AEs (grade 3 nephritis, grade 4 diabetes
					• No significant changes in serum cytokine or chemokine concentrations
					• No patients discontinued treatment due to AEs or disease progression

Awadalla, 2019[41]	retrospective case control ***(Level IV)***	Patients w solid tumours or Hodgkin lymphoma treated w ICIs: 1. Cases: developed myocarditis 2. Controls: no myocarditis	 101 201	Various	• Influenza vaccination administered to 25% of cases vs 40% of controls (p=0.01) • 36% of vaccinated cases vs 55% of unvaccinated cases had further immune side effects during treatment (p=0.10), including lower rates of pneumonitis (12 vs 36%, p=0.03) • N=47/101 cases experienced major adverse cardiac event during median 175-day follow-up; 24% vaccinated vs 59% unvaccinated cases, p=0.002)
Bersanelli, 2018[42]	multicentre retrospective cohort ***(Level IV)***	Patients w advanced cancer (NSCLC=103, RCC=112, melanoma=55, other=30) treated w ICIs 1. Vaccinated 2. Unvaccinated	 79 221	2016-17 inactivated trivalent or quadrivalent influenza vaccine	• Incidence of influenza=24.1% vaccinated vs 11.8% unvaccinated (OR=2.4; 95% CI 1.23–4.59, p=0.009) • In NSCLC subgroup, incidence of influenza=27% vaccinated vs 17% unvaccinated (OR=1.81; 95% CI 0.67–4.86, p=0.29) • In elderly subgroup (>71 yrs., N=103), incidence of influenza=37.8% vaccinated vs 6.1% unvaccinated (OR=9.28, 95% CI 2.77–31.14, p<0.0001) • No significant differences seen in response rate, disease control rate, or time to treatment failure b/n vaccinated vs unvaccinated patients or b/n patients developing vs not developing influenza

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Strowd, 2018[43]	prospective cohort ***(Level III)***	CNS tumours (high-grade glioma=23, CNS lymphoma=3, meningioma =1) treated w RT, CT, or glucocorticoids	27	2013-14 inactivated quadrivalent high-dose influenza vaccine	• No grade III-IV toxicity reported • Seroconversion rates for A/H1N1=65%, A/H3N2=69%, and B strains=50%, and all significantly higher than 2014 study (p<0.04) • Baseline seroprotection in ≥67% of patients; rose to ≥93% to all strains and remained stable at 3 mos. post-vaccination • Seroconversion universally poor in patients w post-treatment lymphopenia
Wijn, 2018[44]	retrospective cohort ***(Level IV)***	Patients w NSCLC treated w nivolumab: 1. Vaccinated 2. Unvaccinated	 42 85	2015-16 or 2016-17 trivalent inactivated influenza vaccine	• Incidence of irAEs = 26% vaccinated vs 22% unvaccinated patients (rate ratio 1.20, 95% CI 0.51-2.65) • Incidence of serious irAEs = 7% vaccinated vs 4% unvaccinated patients (rate ratio 2.07, 95% CI 0.28-15.43) • No significant differences in rates of discontinuation, death, clinical deterioration, or tumour response between groups
Bitterman, 2018[45]	systematic review ***(Level I)***	6 studies conducted between 2013-2017 including adults w hematologic and solid tumours	2275	Various	• Observational data suggest lower mortality and infection-related outcomes w vaccination • Evidence, although weak, shows benefits overweigh potential risks when vaccinating adults w cancer against influenza • No conclusive evidence re. use of adjuvanted versus non-adjuvanted influenza vaccine in this population
Waqar, 2018[46]	prospective cohort ***(Level III)***	Patients w non-hematologic malignancies receiving CT: 1. Vaccinated on day of CT 2. Vaccinated 1 wk. before CT	 8 10	2011-12 trivalent inactivated influenza vaccine	• Seroconversion against H1N1, H3N2, and B strains observed in 63% (5/8), 50% (4/8), and 38% (3/8) of patients in group 1, and 50% (5/10), 70% (7/10), and 60% (6/10) in group 2 • Seroconversion and seroprotection rates against 3 influenza strains not significantly different b/n groups • All patients (8/8) vaccinated in group 1 demonstrated seroprotection to at least 1 strain, compared w 60% of patients in group 2 • Seroprotection rates 50% for all 3 strains in group 1, and 20% (2/10), 40% (4/10), and 50% (5/10) for strains H1N1, H3N2, and B, respectively in group 2
Läubli, 2018[47]	prospective trial ***(Level III)***	1. Patients w lung cancer receiving ICIs 2. Age-matched healthy controls	23 11	Inactivated, unadjuvanted trivalent vaccine containing: Influenza/A/H1N1/California/2009, Influenza/A/H3N2/Texas/2012, Influenza/B/Brisbane/2008	• No significant differences between patients and healthy controls in vaccine-induced antibody titers against all 3 viral antigens • Vaccination resulted in protective titers in more than 60% of patients/ participants • Post-vaccine frequency of irAEs 52.2% w median time to occurrence of 3.2 mos. after vaccination • 6/23 patients (26.1%) showed severe grade 3 or 4 irAEs, including N=2 colitis, N=2 encephalitis, N=1 peripheral neuropathy, N=1 pneumonitis; other AEs included N=3 rash, N=3 arthritis, and N=1 hypothyroidism
Branagan, 2017[48]	prospective trial ***(Level III)***	Patients w multiple myeloma (N=49) or Waldenstrom's Macroglobulinemia (N=2); 41 patients had disease requiring therapy	51	Two doses of 2014-15 trivalent Fluzone® high-dose influenza vaccination, administered 30 days apart	• Total seroprotection rate against all 3 influenza strains = 4% at baseline, 47% after initial dose (p < 0.001), and 65% after second dose (p<0.01) • Seroconversion rates after initial dose: 69% (35/51) H3N2, 73% (37/51) H1N1, 67% (34/51) influenza B, and 39% (20/51) combined strains • Seroconversion against influenza B improved significantly after second dose (67% to 96%, p < 0.001) and seroconversion against

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					all three strains increased from 39% to 55% after second vaccination (p=0.02) • Rate of laboratory-confirmed influenza infection=6%
Nakashima, 2017[49]	prospective cohort ***(Level III)***	Patients w lung cancer undergoing CT (25) or COPD (controls, 26)	51	2013-14 trivalent inactivated influenza vaccine	• A/H1N1 seroprotection rate=84% lung cancer vs 81% COPD; (not significant) A/H3N2 seroprotection rate=84% lung cancer vs 96% COPD (not significant); B strain seroprotection rate = 64% lung cancer vs 92% COPD (p=0.019) • Patients w lung cancer receiving platinum doublet treatment exhibited lower seroprotection rates than those receiving single agent
Keam, 2017[50]	randomized controlled trial ***(Level II)***	Breast & lung cancer patients receiving CT: 1. Vaccinated on day 1 of CT cycle 2. Vaccinated on day 11 of CT cycle	 43 54	2014-15 trivalent inactivated influenza vaccine	• Seroprotection rates day 1 group vs day 11 group: H1N1, 67% vs 75%, p=0.403; H3N2, 77% vs 80%, p=0.772; strain B, 21% vs 27%, p=0.472 • Seroconversion rates day 1 group vs day 11 group: H1N1, 41% vs 57%, p=0.151; H3N2, 44% vs 52%, p=0.429; strain B, 10% vs 18%, p=0.306 • AEs day 1 group vs day 11 group = 13% vs 32%, p=0.040
La Torre, 2016[51]	systematic review and meta-analysis ***(Level I)***	22 studies conducted between 1993-2016 including adult and pediatric patients w hematologic malignancies	N/A	Various	• Protection rate of H1N1 booster dose=30% (95% CI=6-62%) • Pooled prevalence protection rate available for meta-analysis only for first dose = 42.6% (95% CI=23.2–63.3 %) for H3N2 and 39.6 % (95% CI=26%- 54.1%) for B strain • Response rate of booster dose=35% (95% CI=19.7-51.2%) for H1N1, 23% (95% CI=16.6-31.5%) for H3N2, and 29% (95% CI=21.3- 37%) for B strain
Sanada, 2016[52]	multicentre prospective trial ***(Level III)***	Patients w solid tumours or hematologic malignancies receiving CT	109	2013-14 trivalent inactivated influenza vaccine; second vaccinations administered to patients who did not respond to all 3 viral strains after first vaccination	• Proportion of patients w protective titres against all 3 viral strains increased from 3 to 27% following vaccination (p< 0.01) • 79 patients received a second vaccination; proportion of those w • protective titres against individual strains increased by 10% (H1N1), 8% (H3N2), and 3% (B) from first vaccination • No serious AEs observed
Sun, 2016[53]	prospective cohort ***(Level III)***	CLL patients treated w ibrutinib	19	2013-14 trivalent inactivated influenza vaccine	• Seroconversion rates for A/H1N1, A/H3N2, and B strains = 16%, 26%, and 11%, respectively • Significant increases in GMTs for all three strains • Significant increase in seroprotection rate for A/H3N2 (32% vs 74%, p=0.004) • 7 patients developed influenza-like illness w/n 6 mos. of immunization
Jamshed, 2016[54]	randomized controlled trial ***(Level II)***	Cancer patients <65 yrs. receiving CT: 1. Standard dose influenza vaccine 2. High-dose influenza vaccine	 51 54	2012-13 (year 1) and 2013-14 (year 2) trivalent inactivated influenza vaccines	• No severe AEs reported • Seroconversion rates for all 3 influenza antigens and post-vaccination GMTs for H3N2 and B strains significantly improved in patients receiving high-dose vs standard-dose
Berglund, 2014[55]	prospective trial ***(Level III)***	Cancer outpatients receiving ongoing treatments w CT, monoclonal antibodies,	96	2009 influenza A(H1N1) AS03-adjuvanted split virion vaccine x 2 doses + 2009 trivalent non-adjuvanted seasonal influenza vaccine x 1 dose	• 100% (N=13) of patients treated w rituximab did not respond to immunization • For patients not treated w rituximab:

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
		tyrosine kinase inhibitors or corticosteroids			○ H1N1 vaccine: seroconversion = 84% (N=63), seroprotection = 87% (N=65) ○ Seasonal influenza vaccine (A/Bri): seroconversion = 42% (N=28), seroprotection = 70% (N=46) • Seasonal influenza vaccine (A/Uru): seroconversion = 50% (N=33), seroprotection = 59% (N=39)
Strowd, 2014[56]	prospective cohort ***(Level III)***	CNS tumours (GBM = 21, high-grade gliomas = 5, low-grade gliomas = 6, primary CNS lymphoma = 6) treated w CT, RT, +/- glucocorticoids	38	Seasonal trivalent inactivated influenza vaccine	• At 28 days post-vaccine, seroconversion rates for A/H1N1, A/H3N2, and B strains = 37%, 23%, and 23%, respectively; seroprotection rates = 80%, 69%, and 74%, respectively
Vinograd, 2013[57]	prospective non-intervention trial ***(Level III)***	patients w solid tumours receiving CT and hematologic patients w active disease	806	2011 seasonal trivalent killed influenza vaccine	• Immunization rate=387/806 (48%) • Hospitalization rate for fever or acute respiratory infections, pneumonia, and/or infection-related CT interruptions = 111/387 (28.7%) vaccinated patients vs 112/419 (26.7%) unvaccinated patients (p=0.54) • Mortality rate = 46/387 (11.9%) vaccinated patients vs 80/419 (19.1%) unvaccinated patients (p= 0.005)
Chu, 2013[58]	prospective trial ***(Level III)***	Ovarian cancer: 1. In remission receiving a dendritic cell vaccine ± cyclophosphamide 2. In remission not receiving treatment 3. Undergoing standard therapy	31	Seasonal trivalent killed influenza vaccine	• 4-fold response for H1N1 in 20% of patients, for H3N2 in 26% of patients, and for influenza B in 6% of patients • Pre-existing exposure to influenza predictive of responders
Lagler, 2012[59]	prospective trial ***(Level III)***	1. Hematologic malignancies + cytotoxic, targeted, or hormone therapy 2. Solid tumours + cytotoxic, targeted, or hormone therapy 3. Healthy controls	25 17 23	Unadjuvanted whole-virion pandemic influenza A (H1N1) vaccine	• 260/285 (91.2%) patients w solid tumours who offered free immunization during their therapy declined • Seroprotection: 96% healthy, 90% solid tumours, 67% hematologic malignancies (p<0.05) • Seroconversion: 70% healthy, 52% solid tumours, 13% hematologic malignancies (p<0.05) • GMT ratios: 4.1healthy, 4.3 solid tumours 1.5 hematologic malignancies (p<0.05)
Mariotti, 2012[60]	prospective trial ***(Level III)***	1. Hematologic malignancies 2. Healthy controls	47 77	Monovalent adjuvanted 2009 H1N1 vaccine	• At 28 days post-vaccine, rates of seroprotection (95.2% vs 75.2%, p<0.01) and seroconversion (88.7% vs 51.1%, p<0.01), as well as GMT (256 v. 134, p<0.05), lower for pts w hematologic malignancies vs health controls • Patients not receiving CT had seroprotection and GMTs like controls in all time points, while patients receiving CT or allogeneic HSCT had lower seroprotection and seroconversion levels than controls on day 28 and 50
Hottinger, 2012[61]	prospective controlled open label ***(Level III)***	1. Lymphoma and solid tumours (34.5% active CT) 2. Healthy controls	197 138	AS03A-adjuvanted split influenza A/H1N1/09 vaccine x 2 doses for cancer patients and x 1 dose for healthy controls	• Seroprotection: 87.4% cancer patients vs 87% controls (p=0.16) • Seroconversion: 82.3% cancer patients vs 87% controls (p=0.33)

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					• Active CT (p=0.01), lymphoma (p=0.03), rituximab (p<0.001), and steroid treatment (p=0.02) associated w lesser antibody responses in cancer pts
Xu, 2012[62]	prospective case series ***(Level IV)***	1. Healthy controls 2. Solid tumour + myelosuppressive CT 3. Solid tumour + non-myelosuppressive CT 4. Hematologic	44 38 42 22	Monovalent unadjuvanted influenza A (H1N1) 2009 vaccine	• Seroprotection: 95.5% group 1, 75% group 2, 90.5% group 3, 90.1% group 4; no significant differences between groups • Seroconversion: 80% group 1, 72.2% group 2, 87% group 3, 75% group 4; no significant differences b/n groups
Rousseau, 2012[63]	prospective cohort ***(Level III)***	Patients receiving cytotoxic and/or targeted therapies	65	AS03A-adjuvanted H1N1v vaccine x 1 or 2 doses	• Seroprotection: 48% after one dose; 73% after two doses • Seroconversion: 44% after one dose; 73% after two doses • Vaccine-related AEs mild to moderate
Puthillath, 2011[64]	prospective case series ***(Level III)***	Colorectal cancer: 1. CT 2. No CT	 58 27	2006-2007 trivalent influenza vaccine x 1 dose	• Immune response: 70.6% overall population, 69% CT group, 74.1% non-CT group (OR=0.78; p=0.8) • Seroconversion: 12.1% CT group vs 11.1% non-CT group • No difference in responses by chemo regimen or timing of immunization w regards to CT administration
Miraglia, 2011[65]	multicentre prospective cohort ***(Level III)***	Cancer (tumour type not specified) compared to elderly and immuno-compromised patients	319	Monovalent unadjuvanted influenza A (H1N1) 2009 vaccine	• Seroprotection: 52.4% (95% CI: 46.7–57.9) • Seroconversion: 49.2% (95% CI: 43.6–54.8) • No comparisons made by tumour type or CT regimen
Yri, 2011[66]	prospective controlled trial	1. Lymphoma treated w rituximab ± CT 2. Healthy controls	67 51	Monovalent adjuvanted influenza A (H1N1) vaccine x 1 dose	• Seroprotection: 0% lymphoma vs 82% controls
Monkman, 2011[67]	prospective cohort ***(Level III)***	Hematologic malignancies: 1. Vaccinated 2. Unvaccinated	 62 41	AS03A-adjuvanted H1N1 vaccine x 1 dose	• Seroconversion: 21% vaccinated vs 0% unvaccinated (p<0.001) • Seroprotection: 40% vaccinated vs 22% unvaccinated (p=0.058) • 10/46 vaccinated patients on active CT seroconverted and 16/46 mounted seroprotective titers • 2/12 vaccinated patients on active rituximab seroconverted and 4/12 mounted seroprotective titers • 1/3 vaccinated stem cell transplant recipients seroconverted • No differences in response rates between patients on or off CT, on or off rituximab, or between pts w lymphoid vs non-lymphoid malignancies
de Lavallade, 2011[68]	prospective cohort ***(Level III)***	1. Hematological (B-cell malignancies, CML, and ASCT recipients) 2. Healthy controls	97 25	AS03A-adjuvanted H1N1v vaccine x 1 dose + trivalent seasonal influenza vaccine x 1 dose	• Seroprotection day 21: 100% controls vs 39.3% B-cell malignancies (p<0.001), 45.5% ASCT recipients (p<0.001), 85.0% CML (p=0.086); rates in CML patients significantly higher vs B-cell malignancies (p=0.003) and ASCT recipients (p=0.011) • Seroprotection day 49: 100% controls vs 67.9% B-cell malignancies (p=0.002), 72.7% ASCT recipients (p=0.008), 95.0% CML (p=0.46) • Seroconversion day 21: 100% controls vs 35.7% B-cell malignancies (p<0.001), 45.5% ASCT recipients (p<0.001), 80% CML (p=0.036) • Seroconversion day 49: 100% controls vs 64.3% B-cell malignancies (p=0.001), 72.7% ASCT recipients (p=0.008), 90% CML (p=0.20)

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					• Adverse reactions in 90.5% of hematology patients and 88% of controls; 2.1% and 3.2% of local and systemic reactions in hematology patients respectively rated as severe
Loulergue, 2011[69]	prospective cohort ***(Level III)***	1. Breast – docetaxel 2. Prostate – docetaxel	13 12	Trivalent inactivated influenza vaccine x 1 dose	• Seroconversion: 28% (95% CI: 23.1-33.3 ; H1N1), 8% (95% CI: 7.7-8.3; H3N2), 16% (95% CI: 7.7-25; B strain) • GMT: 2.16 (H1N1), 1.3 (H3N2), 1.58 (B) • No serious AEs related to vaccine
Mackay, 2011[70]	prospective cohort ***(Level III)***	1. Hematologic malignancies 2. Solid tumours	26 20	pH1N1 vaccine x 1 dose	• Seroprotection: 50% vs 27% (solid vs hematologic; p=0.11) • Seroconversion: 45% vs 19% (solid vs hematologic; p=0.06); addition of rituximab resulted in failure to convert (p=.05) • Highest titres: mid-cycle immunization in pts w/solid tumours and start of cycle for hematological patients • Immunization well tolerated
Sasson, 2011[71]	prospective cohort ***(Level III)***	Palliative care patients	13	Trivalent influenza vaccine Vaxigrip x 1 dose	• Seroprotection: increased from 15.4% to 61.5% after immunization • Serum response: 53.8% for all 3 strains of vaccine • GMT: from 8.3 to 159.4 after immunization for A-H3N2; from 5.2 to 124.3 for A-H1N1; from 5.7 to 44.6 for influenza B
Stadtmauer, 2011[72]	randomized controlled trial ***(Level II)***	Multiple myeloma	21	1. Influenza-primed autologous T-cell product (HSCT) Nonspecifically primed autologous T-cell product (HSCT)	• Seroconversion: influenza-primed autologous T-cell product group more likely to respond to influenza vaccine (P=.001) • No differences in global quantitative recovery of T-cell and B-cell subsets or in global T-cell and B-cell function
Chadha, 2011[73]	prospective cohort ***(Level III)***	Prostate cancer	35	Trivalent influenza vaccine (Fluzone) x 1 dose	• Serological response (against any strain): 80% • Effect of vitamin D: baseline 25-D3 level associated w response (p=.045) and all upper quartile 25-D3 patients responded (p=.034)
Mulder, 2011[74]	case control ***(Level IV)***	1. mRCC - sunitinib 2. mRCC - sorafenib 3. mRCC - no CT 4. Healthy controls	16 6 7 11	Seasonal influenza inactivated vaccine x 1 dose	• Seroprotection: similar between sunitinib and sorafenib vs controls • Functional T-cell reactivity: sorafenib patients had a decreased rate of proliferation, decreased IFN-γ/IL-2, and increased IL-10 vs controls
Bedognetti, 2011[75]	case control ***(Level IV)***	1. Non-Hodgkin lymphoma – post rituximab 2. Controls	31 34	Trivalent seasonal influenza vaccine x 1 dose	• Response: lower in patients vs controls for each strain, especially in patients treated w fludarabine (European immunogenic criteria not met); CD27(+) memory B-cells reduced among patients vs controls
Meerveld-Eggink, 2011[76]	randomized controlled trial ***(Level II)***	1. Breast cancer – FEC CT 2. Healthy controls	38 21	Influenza vaccine administered either early (day 4 of chemo; n=20) or late (day 16 of chemo; n=18)	• Response rate: significantly lower in patient group vs controls; early group had higher antibody titers vs late group (not sig) • GMT: 63.7 vs 29.5 (early vs late, H3N2), 28.2 vs 19.6 (early vs late, H1N1), 29.8 vs 16.0 (early vs late, B/Brisbane) • Subgroup analysis performed in 2017 reported broad serum antibody response to influenza virus vaccine in patients treated w CT for breast cancer
Avetisyan, 2008[77]	case-control ***(Level IV)***	1. Healthy volunteers 2. Allo-SCT patients	18 14	Inactivated trivalent 2005/2006 influenza vaccine x 1 dose	• 29% of SCT patients demonstrated protective antibody levels to influenza A H1N1 serotype • Critical period is later than 90 days post-SCT, when patients gradually return to contact w community and are more exposed to infection by circulating respiratory viruses • Authors recommend influenza immunization 3 mos. or longer after allo-SCT, as long as no GVHD or ongoing immunosuppression

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations

Ljungman, 2005[78]	open, randomized ***(Level II)***	Hematologic malignancies (N=59 receiving active CT against malignancy)	36
			34
				1. one-dose vaccine
				2. two-doses vaccine
				
				Min. 1 wk. b/n immunization and next scheduled CT course
					• Response rates:
					  ○ H1N1:14/70 (20%)
					  ○ H3N2: 14/70 (20%)
					  ○ Influenza B: 16/70 (23%)
					• 4/70 patients responded and became immune to all three influenza subtypes after immunization
					• Proportion of immune patients after 1-dose vs 2-doses:
					  ○ H1/N:1 25% vs 26% (NS)
					  ○ H3/N2: 22% vs 21% (NS)
					  ○ Influenza B: 14% vs 18% (NS)
					• Patients w myeloproliferative disorders responded better to H1N1 vs multiple myeloma patients (p=.002) and patients w lymphoma also responded better than patients w multiple myeloma (p<.001)
					• Trend for better responses in patients w less intensive CT
					• Authors recommend immunization of family members and hospital staff

Machado, 2005[79]	prospective cohort ***(Level III)***	Hematologic malignancies:
		1. < 6 mos. post-BMT, not eligible for immunization
		2. > 6 mos. post-BMT
			
			134
			
			43
				Trivalent seasonal influenza vaccine x 1 dose	• 25/134 (18.6%) in group 1 developed influenza
					• 19/43 (44.2%) in group 2 vaccinated, and vaccine efficacy 80%
					• 12/24 (50%) unvaccinated in group 2 developed influenza
					• Multivariate analysis:
					  ○ Seasonal exposure and conditioning regimens independently associated w increased risk for influenza
					  ○ influenza vaccine and steroid therapy showed a protective role
					• Gender, BMT type, underlying disease and GVHD not associated w risk of influenza infection

Earle, 2003[80]	retrospective cohort ***(Level IV)***	1. Stage IV colorectal cancer patients who received seasonal influenza vaccine 2. Stage IV colorectal cancer patients not immunized	626 951	Seasonal influenza vaccine	• SEER database and Center for Medicare and Medicaide Services database accessed for immunization rates among patients undergoing CT in September – December between 1993-1996 • Patients who developed influenza while undergoing CT: 3.8% unvaccinated vs 1.1% vaccinated, p=.004 • Influenza immunization associated w HR for death of 0.88 (95% CI, 0.77-0.99) • 68% of patients immunized received immunization through primary care physician, yet oncologists often these patients' most consistent medical contacts. Critical that oncologists actively provide routine influenza immunization to patients w advanced cancer as part of delivering comprehensive, high-quality cancer care
Nordoy, 2002[81]	case-control ***(Level IV)***	1. Solid tumours or malignant lymphoma; mild-moderate immunosuppressive CT 2. Healthy controls	35 38	Trivalent inactivated seasonal influenza vaccine x 1 dose + 23-valent polysaccharide pneumococcal vaccine	• After 1 immunization, 25 patients (72%) and 34 controls (87%) serologically protected against 2 of the 3 flu strains • Higher proportion of patients w solid tumours (81%) than lymphoma (38%) achieved protection • Age, duration of CT, and curative vs palliative treatment did not influence immunization response

aOR, adjusted odds ratio; AEs, adverse events; ASCT, allogeneic stem cell transplantation; BMT, bone marrow transplant; CCI, Charlson comorbidity index; CI, confidence interval; CML, chronic myelogenous leukemia; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; GBS, Guillain-Barre Syndrome; GMT, geometric mean titer; GVHD, graft-versus-host-disease; HR, hazard ratio; ICI, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; IRR, incidence rate ratio; LRTI, lower respiratory tract infection; MM, multiple myeloma; MPN, myeloproliferative neoplasm; OR, odds ratio; OS, overall survival; PFS, progression free survival; RT, radiotherapy; SCT, stem cell transplant; SEER, Surveillance, Epidemiology, and End Results; UICC, Union for International Cancer Control; VAERS, Vaccine Adverse Event Reporting System

Table 3: Summary of Peer-Reviewed Literature on Influenza Immunization in Pediatric Patients with Cancer, Jan. 2000 – Sep. 2024

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Doganis, 2018[82]	prospective cohort ***(Level III)***	Patients w leukemia (48), lymphoma (5), and solid tumours (22); median age = 8.8 yrs.	75	Inactivated trivalent seasonal vaccine	• Protective rates after vaccination = 79% H1N1, 75% H3N2, 59% influenza B • Seroconversion rates = 54% H1N1, 44% H3N2, 43% influenza B • Variables that correlated w higher post-vaccination seroprotective titer: ALC >1000/mm3 for H1N1, age >9 yrs., or solid tumors for H3N2 and B strains • Variables that correlated w significantly higher seroconversion rate: solid tumours and prevaccination HAI≥40 Variables that significantly correlated w higher post-vaccination GMTs: GMTs before vaccination, high ALC at vaccination time, and solid tumours for H1N1; GMTs before vaccination and solid tumours also significant factors for higher post-vaccination GMTs for H3N2 and influenza B
Sykes, 2017[83]	retrospective cohort ***(Level IV)***	Patients w acute leukemia treated on the TOTALXVI protocol; median age = 6 yrs.	498	2011-12, 2012-13, and 2013-14 inactivated trivalent seasonal vaccines	• 354/498 vaccinated (71.1%) and 98 given booster dose (19.7%) • No difference in overall rates of influenza between vaccinated and unvaccinated patients overall or in any season • No difference in rates of influenza between patients who received 1 dose vs 2 doses of vaccine No difference in time to first influenza infection in vaccinated vs unvaccinated patients
de de la Fuente Garcia, 2017[84]	retrospective cohort ***(Level IV)***	Children treated for ALL between 2000-2012; median age = 4.1 yrs.	60	Booster dose of inactivated conjugated Haemophilus influenza B given at least 3 mos. after end of CT	• Seroprotection rate at end of CT = 20% • Seroprotection rate after booster dose administered = 92% During previous influenza season, 18 mothers (40.0%), 19 fathers (42.2%), and 16 siblings (35.6%) had received seasonal influenza vaccine
Choi, 2016[85]	prospective cohort ***(Level III)***	Patients receiving CT for solid tumours (76) and hematologic malignancies (183) studied over 2 yrs.	259	2012-13 trivalent inactivated influenza (N=112) vaccine and 2013-14 quadrivalent inactivated influenza vaccine (N=147)	• Seroresponse rate = 62% (98/157) • Median ALC at vaccination higher in seroresponders than nonresponders (854 cells/mm^3 vs 602 cells/mm^3, p< 0.036) • Patients w ALC <1,000 cells/mm^3 at time of vaccination twice as likely to be serononresponders (OR = 2.4, 95% CI 1.1-5.0; p<0.02) 31/259 (12%) of patients developed influenza: 31/31 had fever at presentation, 8/31 required hospitalization, and 25/31 had CT delays
Hakim, 2016[86]	randomized open-label trial ***(Level II)***	Children and young adults (3-21 yrs.) w leukemia (27), solid tumours (17), or HIV (41)	85	Two doses of high-dose (HD) TIV vs two doses of standard-dose (SD) TIV; doses administered 21 days apart	• Leukemia patients receiving HD TIV had significantly greater increase in HAI titers to B antigen versus leukemia patients receiving SD TIV • Solid tumour patients receiving HD TIV had significantly greater increase in HAI titers to H1 antigen versus solid tumour patients receiving SD TIV • No differences in seroconversion or seroprotection rates between HD • TIV and SD TIV in all groups • No significant difference in reactogenicity events in recipients of HD TIV (54% after dose 1, 38% after dose 2) versus SD TIV (40% after dose 1, 20% after dose 2)
Kotecha, 2016[87]	prospective cohort ***(Level III)***	Children ww hematologic and solid tumours aged 6 mos. to 18 yrs. receiving or w/n 4 wks. of completion of CT	100	2010-11 trivalent inactivated vaccine: A/Perth/16/2009, A/California/7/2009, and B/Brisbane/60/2008	• Seroprotection rates = 55% H3N2, 61% H1N1, 41% B strain • Seroconversion rates = 43% H3N2, 43% H1N1, 33% B strain • Significant response observed for H3N2 (Geometric Mean Fold Increase = 4.56, 95% CI 3.19–6.52, p< 0.01) and H1N1 (GMFI = 4.44, 95% CI 3.19–6.19, p< 0.01) • Children w solid tumors significantly more likely to serorespond to each vaccine strain compared to children w hematologic malignancies ○ H3N2: OR=7.39, 95% CI 2.42–22.53, p< 0.01

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					○ H1N1: OR=2.90, 95% CI 1.02–8.23, p=0.045 ○ B strain: OR=3.75, 95% CI 1.25–11.24, p= 0.02 Children w solid tumours significantly more likely to undergo complete seroconversion to all three strains (OR=6.03, 95% CI 1.56–23.29, p< 0.01) compared to children w hematological malignancies
Ottóffy G, 2014[88]	prospective cohort ***(Level III)***	Patients receiving CT for solid tumours (15) and hematologic malignancies (12)	27	Inactivated, whole-virion, adjuvanted pandemic H1N1 vaccine administered simultaneously w 2009 seasonal influenza vaccine x 1 dose	• Pre- and post-immunization seroprotective rates H1N1: 33–48%, H3N2: 56–78%, influenza B: 0–15% for seasonal influenza, and for pandemic H1N1: 15–37% • Seroresponse rates for seasonal influenza H1N1, H3N2, and B 22%, 37%, and 22%, respectively, and 30% for pandemic H1N1 vaccine • Determinants of responsiveness lymphocyte count and serum immunoglobulin-G • Only influenza B vaccine elicited significant differences in differences in pre- and post-immunization seroprotective rates
McManus M, 2014[89]	randomized, double-blind, phase I safety trial ***(Level II)***	ALL (80% on maintenance therapy)	34 16	1. High-dose TIV (60 µg) 2. Standard-dose TIV (15 µg)	• no significant differences reported in local or systemic symptoms • No severe AEs attributed to vaccine No significant differences in immune response between high- and standard-dose TIV groups
Dotan, 2014[90]	prospective cohort ***(Level III)***	Patients w leukemia (16), lymphoma (10), neuroblastoma (4), and other malignancies (10) admitted to hospital w fever +/- other influenza A or H1N1 symptoms	40	Vaccinated patients received Pandemrix-influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) before hospitalization	• 57 total episodes; 13/57 (22.8%) influenza A/H1N1 positive • 2/13 (15%) H1N1-positive episodes previously immunized versus 14/44 (32%) H1N1-negative episodes (p=0.3) • No sig demographic differences between groups w and w/o influenza A/H1N1 infection; no difference in proportion who received CT in influenza A/H1N1-positive group vs H1N1-negative group (69.2% vs 65.1% (p=0.8) • Proportion of children who underwent BMT= 7.7% in influenza A/H1N1-positive children vs 4.8% in influenza A/H1N1-negative children 7/16 (44%) episodes in vaccinated children presented w fever and URI symptoms vs 24/41 (59%) episodes in unvaccinated children (p=0.38)
Goossen, 2013[91]	meta-analysis (Cochrane Review) ***(Level I)***	Pediatric malignancies	770	• 9 controlled clinical trials and 1 RCT included in review • In 5 studies, immune responses to influenza vaccine compared in 272 children on CT w 166 children not on CT • In 4 studies, responses to influenza vaccine assessed in 236 children on CT compared w responses in 142 healthy children • Immune responses in children receiving CT consistently weaker (four-fold rise of 38% to 65%) than in those children who had completed CT (50% to 86%) and in healthy children (53% to 89%) • AEs included mild local reactions and low-grade fever; no persistent or life-threatening effects reported • Authors concluded that although pediatric oncology patients receiving CT can generate an immune response to influenza vaccine, it is unclear whether this immune response protects them from influenza infection or its complications	
Leahy, 2013[92]	prospective cohort ***(Level III)***	ALL	45	Patients received 2 doses of inactivated split-virion AS03-adjuvanted vaccine. Serological response measured before each vaccine dose (days 0 & 28) and 3 mos. after second dose.	• Pre and post titres available from 45 children after 1 vaccine dose and 39 children after 2 doses. Seroconversion rates 11.1% after 1 dose and 25.6% after 2 doses. • Significantly higher (p= 0.01) seroconversion rate among children who received adult vaccine dose (0.5 ml) in univariate analyses, and a trend towards significance (p=0.07) in multivariate analyses. • Factors including age, gender, lymphocyte count, treatment phase and regimen did not significantly affect seroconversion rate.

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					Children who received adult dose demonstrated significantly greater magnitude of serological response after 1 dose (p=0.04) and 2 doses (p=0.001).
Mavinkurve-Groothuis, 2013[93]	prospective cohort ***(Level III)***	Children w hematologic malignancies (20) or solid tumours (11) treated w CT or w/n 6 mos. after end of CT	31	Inactivated split-virion preparation of A/California/07/2009(H1N1)v-like strain x 2 doses (3-wk. interval)	• No sig. difference in immunization response between patients w hematologic cancer vs solid tumours. • Sig. difference in absolute lymphocyte count prior to first immunization b/n patients w protective vs no protective response (p= 0.012). • Absolute lymphocyte counts for above lower normal limits (LNL) for age seen in 13/28 patients (46%). In 12/13 patients (92%), a protective response to immunization seen. In 15 patients w absolute lymphocyte counts below LNL for age, only 5 (33%) had a protective response to immunization (p=0.002). No protective immunization response observed in patients w $CD4^+$ T cell count less than 200/mm^3.
Karras, 2012[94]	randomized trial ***(Level I)***	Vaccine-naïve patients >60 days post- allogeneic HSCT	33 32	Single dose inactivated trivalent seasonal influenza vaccine (H3N2 + H1N1pdm09 +influenza B Victoria lineage) vs Double dose inactivated trivalent seasonal influenza vaccine (H3N2 + H1N1pdm09 +influenza B Victoria lineage), separated by 1 mo.	• Seroprotection: no significant differences at 8 wks. for H3N2 (19% 1-dose vs 19% 2-doses), H1N1 (32% 1-dose vs 32% 2-doses), and influenza B (32% 1-dose vs 23% 2-doses) • Seroconversion: no significant differences at 8 wks. for H3N2 (13% of 1-dose vs 22% 2-doses), H1N1 (31% 1-dose vs 31% 2-doses), and influenza B (16% 1-dose vs 25% 2-doses) No patients vaccinated <1 yr. from SCT showed seroconversion to H3N2 virus vs 39% of patients vaccinated ≥1 yr. (p=0.001); similarly, only 6% and 8% of patients in <1 yr. group seroconverted to H1N1 and influenza B, respectively, whereas 64% (p=0.001) and 39% (p=0.003) seroconverted in ≥1 yr. group
Kersun, 2012[95]	prospective cohort ***(Level III)***	ALL	177	Inactivated trivalent influenza vaccine x dose in repeat vaccines and x 2 doses in vaccine-naïve patients	• Patients vaccinated during induction phase had superior vaccine responses compared to patients vaccinated during post-induction or maintenance phases (p=0·0237). • Higher aggregate HAI titer responses associated w higher baseline B-cell count (p=0·0240), and higher CD4 and CD8 influenza-specific T-cell responses, suggesting prior antigen exposure is a significant contributor.
Wong-Chew, 2012[96]	prospective cohort ***(Level III)***	AML, solid tumours, or lymphoma	56	Inactivated trivalent seasonal vaccine	• Seropositivity from pre- to post-vaccine: 43% to 63% for H1N1 serotype (p=0.02), 68% to 85% for H3N2 serotype (p=0.05) and 0% to 14% for B serotype (p=0.006) • GMT from pre- to post-vaccine: 47 (95% CI, 128-378) to 138 (95% CI, 363-685) for H1N1 virus (p=0.009), 99 (95% CI, 208-485) to 277 (95%, CI, 466-775; p=0.009) for H3N2 virus, and 10 (95% CI, 9-10) to 14 (95% CI, 5-58) for influenza B virus (p=0.11)
Shahin, 2012[97]	prospective cohort ***(Level III)***	Patients receiving CT for solid tumours	20	AS03-adjuvanted or nonadjuvanted monovalent vaccine x 2 doses at day 0 and 21; most often administered on day 1 of CT	• Seroprotection: 90% • Seroconversion: 65% 8.8-fold increase in GMT from pre- to post-vaccine
Hakim, 2012[98]	prospective observation ***(Level IV)***	Solid and hematological, receiving CT	37	2009 H1N1 influenza monovalent vaccine x 1 or 2 doses (age dependent)	• Seroprotection: achieved in 52% of hematology patents and 75% of solid tumour patients after last dose • Seroconversion: achieved in 48% of hematology patients and 50% of solid tumour patients after last dose • No significant differences in seroconversion or seroprotection rates b/n patients who received one dose versus two doses

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Carr, 2011[99]	randomized trial ***(Level II)***	Solid and hematological, receiving or received CT or RT w/n last 3 mos.	28 27	1. LAIV x 1 or 2 doses TIV x 1 or 2 doses	• Seroprotection: H3N2 (80.7% LAIV vs 92.3% TIV, p=0.41), H1N1 (34.6% vs 73.0%, p=0.01), influenza B (3.8% LAIV vs 15.3% TIV, p=0.34) • Seroconversion: H3N2 (7.6% LAIV vs 46.1% TIV, p<0.004), H1N1 (7.6% vs 26.9%, p=0.13), influenza B (0% LAIV vs 3.8% TIV, p>0.999) Two serious AEs reported (febrile illness and seizure)
Yen, 2011[100]	prospective cohort ***(Level III)***	Solid and hematological, receiving CT	25	2009 H1N1 influenza monovalent vaccine x 1 or 2 doses (age dependent)	• Seroprotection: 52% pre-vaccine; 72% post-vaccine (p=.24) • Sero-response: 32% post-vaccine; greater in pts w/o pre-vaccine seroprotective titer than those w (50% vs 15%, p=.07) and greater in those w lymphocyte counts >1,500/µl (p=.008) GMT: increased post-immunization in patients <10 yrs receiving two immunizations (21.4 to 60.6; p=.025)
Cheng, 2011[101]	prospective cohort ***(Level III)***	Patients receiving CT or completed ≤12 mos	12	Haemagglutinin of influenza A/California/07/2009 (H1N1)-like virus x 2	• Seroprotection: 58% after 1st dose (7/12 patients); 100% after 2nd dose Seroconversion: 41% after 1st dose; 75% after 2nd dose

Bate, 2010[102]	prospective cohort ***(Level III)***	Solid and hematological	54	2009 H1N1 influenza monovalent AS03(B)-adjuvanted vaccine x 2 doses, days 0 and 21	• Seroconversion: 44.4% of patients
					  ○ 33.3% among those w/acute lymphoblastic leukemia
					  ○ 36.4% among those w/lymphoma or other leukemias
					  ○ 66.7% among those w/brain tumors
					  ○ 71.4% among those w/other solid tumours
					  ○ 28.6% among those receiving acute lymphoblastic leukemia maintenance therapy
					Non-factors (multivariate): age, cancer type, and lymphopenia

Bektas, 2007[103]	case series ***(Level V)***	Patients w solid tumours aged 1-18 yrs. on CT or w/n 6 mos. of completing CT	45	2 doses of trivalent split vaccine 1 mo. apart	• Fourfold rise in percentage of post-immunization antibody titers detected for: H1N1 (84.4%), H3N2 (77.8%), and influenza B (60%) • Stratification of patients on active CT vs w/n 6 mos. of completion of CT in terms of fourfold rise in antibody titers showed a statistically significant difference for only influenza B (p = .34) • Post-immunization protective rates 86 to 97%
Matsuzaki, 2005[104]	controlled clinical trial ***(Level IV)***	Pediatric malignancies	44	2 doses of influenza vaccine 2-4 wks. apart	• Response rates: H1N1 65%; H3N2 40%; influenza B: 46% • Patients on CT showed a significantly lower response than those immunized after completing CT; protection titers: H1N1=42% vs 90% (p=.006), H3N2=25% vs 83% (p=.019) • For influenza B, patients w low IgG showed a lower response rate than those w higher IgG (29% vs 61%, p=.040) • Multivariate analysis showed that factors associated w low immune response: H1N1= low IgG (p<.001) and administration of CT (p=.003); H3N2= administration Of CT (p=.008); influenza B= low WBC count (p=.03) and low IgG (p=.030)

Chisholm, 2005[105]	controlled clinical trial ***(Level IV)***	Pediatric patients w solid tumours or lymphoma actively receiving CT or who w/n 6 mos. of completing CT	66	1 or 2 doses of influenza vaccine, in autumn 2001 and/or 2002	• Following immunization:
					  ○ 25/64 patients (38%) protected against all three viruses, representing a full response
					  ○ Protective responses to one or two viral strains seen in 12/64 (19%) patients
					  ○ 27 (41%) patients showed no protective response to immunization, including 5 patients who remained fully susceptible to all 3 viruses following immunization
					• Estimated increases in percentage protected against each viral subtype following immunization:

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					○ H1N1: 29% (95% CI 17–42%, p<.0001) ○ H3N2: 22% (95% CI 10–33%, p=.0002) ○ Influenza B: 43% (95% CI 29–57%, p< .0001) • N= 27 patients transfused w blood and/or platelets during study: ○ N=10 (38%) showed no response ○ N=6 (23%) showed a protective response to 1-2 viral subunits ○ N=10 (38%) protected against all 3 viruses • In multivariate analysis, lymphopenia associated w improved response for H1N1 (OR=11.4, 95% CI 1.11–117.37; p= .041), though authors caution that number of patients w lymphopenia small • No significant difference in response rates among children on treatment and off treatment and by intensity of CT regimen
Porter, 2004[106]	controlled clinical trial ***(Level IV)***	1. ALL in 1st remission, maintenance CT, completed last delayed intensification ≥ 4 wks. earlier 2. Healthy controls	20 49	2001–2002 inactivated trivalent influenza vaccine x 1 dose for children >9 yrs. of age and those previously vaccinated, and x 2 doses (1 mo. apart) for previously unimmunized children or those <9 yrs. of age	Although post-immunization geometric mean titres lower in group 1 versus group 2 children for H1N1 antigen (p<.001), H3N2 antigen (p=.03), and influenza B antigen (p=.003), at least 60% of children w ALL had at least a 4-fold increase in HAI titres to each of influenza antigens
Hsieh, 2002[107]	controlled clinical trial ***(Level IV)***	1. Pts w ALL in maintenance stage; received 6-mercaptopurine + methotrexate, and reinduction wvincristine + prednisolone 2. Pts w asthma 3. Healthy controls previously unvaccinated	25 30 10	TIV x 2 doses for children younger than 8 yrs., 1 dose for children older than 8 yrs.	• group 1 developed significant antibody titers to H3N2 antigen 4 wks. after 2nd immunization • Seroconversion rates after 2 doses of vaccine 57.1 to 84.6% and seroresponse rates b/n 24 and 60% in group 1 • Compared to group 2, group 1 had less seroconversion and lower seroresponse rates to H1N1 • Seroconversion and seroresponse rates to influenza B and H3N2 antigens comparable in group 1 and group 2 children • Antibody response in group 1 children who received reinduction CT suggests that therapy did not impair seroresponse rates

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; BMT, blood and marrow transplant; CI, confidence interval; CML, chronic myeloid leukemia; CT, chemotherapy; FEC, 5-FU + epirubicin + cyclophosphamide; GMT, geometric mean titers; GVHD, graft-versus-host disease; HAI, hemagglutination inhibition; HSCT, hematopoietic stem cell transplant; HR, hazard ratio; IgG, immunoglobulin G; irAE, immune-related adverse event; LAIV, live attenuated influenza vaccine; NS, not statistically significant; OR, odds ratio; RCT, randomized controlled trial; RT, radiotherapy; SCT, stem cell transplant; TIV, trivalent inactivated influenza vaccine; WBC, white blood cells.

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Levels of Evidence

- Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity
- Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity
- Level III – prospective cohort studies
- Level IV – retrospective cohort studies or case-control studies
- Level V – studies without a control group, case reports, or expert opinions

Appendix A: Search Strategy

Database	Date	Search Strategy	Results
PubMed	Sep 10, 2024	1. carcinoma[MeSH Terms] 2. neoplasm[MeSH Terms] 3. cancer[Title/Abstract] 4. tumor[Title/Abstract] 5. tumour[Title/Abstract] 6. ((((carcinoma[MeSH Terms]) OR (neoplasm[MeSH Terms])) OR (cancer[Title/Abstract])) OR (tumor[Title/Abstract])) OR (tumour[Title/Abstract]) 7. influenza A virus[MeSH Terms] 8. influenza B virus[MeSH Terms] 9. influenza, human[MeSH Terms] 10. ((influenza A virus[MeSH Terms]) OR (influenza b virus[MeSH Terms])) OR (influenza, human[MeSH Terms]) 11. immunization[MeSH Terms] 12. vaccination[MeSH Terms] 13. immun*[Title/Abstract] 14. vaccin*[Title/Abstract] 15. (((immunization[MeSH Terms]) OR (vaccination[MeSH Terms])) OR (immun*[Title/Abstract])) OR (vaccin*[Title/Abstract]) 16. (((((immunization[MeSH Terms]) OR (vaccination[MeSH Terms])) OR (immun*[Title/Abstract])) OR (vaccin*[Title/Abstract])) AND (((influenza A virus[MeSH Terms]) OR (influenza b virus[MeSH Terms])) OR (influenza, human[MeSH Terms]))) AND (((((carcinoma[MeSH Terms]) OR (neoplasm[MeSH Terms])) OR (cancer[Title/Abstract])) OR (tumor[Title/Abstract])) OR (tumour[Title/Abstract])) 17. Limit #16 to English, from 2023/8/1 – 2024/12/31 18. Excluded case reports, studies w ≤10 patients, duplicates from 2023, covid 19, non-cancer or non-human subjects (i.e., mice, in vitro), vaccine uptake and equity, vaccine design, unrelated to guideline question (i.e., recommendations, response, timing)	755,798 4,014,998 2,339,405 1,515,156 252,538 5,064,590 50,879 4,798 60,120 85,463 218,544 116,138 3,002,147 451,336 3,253,334 1,102 43 3