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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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Research Questions:

1. What are the recommendations for influenza immunization for adult and pediatric patients with solid tumours or hematologic cancers?
2. What is the current evidence for response to the influenza vaccine among adult and pediatric patients with cancer receiving chemotherapy or other systemic therapy?
3. What is the best timing for administering the influenza vaccine in relation to the therapy cycle for adult and pediatric patients with cancer?

Table 1: Summary of Published Literature on Influenza Immunization in Adult Patients with Cancer, January 2000 – August 2022

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Tsiakos, 2022[1]	systematic review/ meta-analysis ***(Level I)***	Cancer patients receiving immune checkpoint inhibitors	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 • 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
Gogenur, 2021[2]	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

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Spagnolo, 2021[3]	systematic review ***(Level I)***	Cancer patients receiving immune checkpoint inhibitors	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 immune checkpoint inhibitor-related AEs was 28.9% • In 6 studies specifying incidence of grade 3-4 toxicities, pooled incidence was 7.5% • No grade 5 toxicities reported • 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 immune checkpoint inhibitors
Desage, 2021[4]	systematic review ***(Level I)***	Inclusion criteria focused on immune-related AE occurrence in cancer patients treated by immune checkpoint inhibitors 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 immune checkpoint inhibitors 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 immune checkpoint inhibitor treatment seems to induce seroprotective humoral response and may raise immune-related AEs • Influenza vaccination for patients treated w immune checkpoint inhibitors not associated w treatment interruption due to progression or clinical deterioration • Inactivated vaccines not contraindicated in patients with immune checkpoint inhibitor treatment, but larger prospective studies needed, especially w immune checkpoint inhibitors combination therapies
Teh, 2021[5]	randomized controlled trial ***(Level II)***	Patients attending outpatient clinics and those electively admitted for HCT. Aged ≥18 yrs. who were w/n 12 mos following autoHCT Patients randomized 1:1 to high-dose (HD)	68	Vaccines were 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	• 68 patients enrolled (34/arm) w median age 61.5 yrs., majority male (68%) w myeloma (68%) • Median time from autoHCT to vaccination was 2.3 mos • For HD-SD and SD-SD arms, percentages of patients achieving seroprotection were 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, geometric mean titers (GMTs) and GMT ratios, and number of influenza-like illness or laboratory-confirmed influenza not significantly different b/n arms

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		inactivated influenza vaccination (IIV) followed by standard dose (SD) vaccine (HD-SD arm) or 2 SD vaccines (SD-SD arm) 4 wks. apart		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	• 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-autoHCT w either 2-dose vaccine schedules
Bersanelli, 2021[6]	prospective ***(Level III)***	Patients w advanced solid tumours receiving therapy with immune checkpoint inhibitors (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%)	• Study 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) • 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 was, respectively, 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
Aznab, 2021[7]	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 one month of follow-up • Cancer patients recommended to receive flu vaccine annually
Whitaker, 2021[8]	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 were 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

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Alimam, 2021[9]	prospective ***(Level III)***	Patients w diagnosis of Essential Thrombocythaemia, Polycythaemia 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 myeloproliferative neoplasm (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 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
Gatti, 2021[10]	retrospective ***(Level IV)***	Patients receiving immune checkpoint inhibitors	590	Any type of vaccine against influenza virus	• Over observed period, out of total of 712,776 AEs following immunization (AEFI), 191 (0.03%) reports of myopericarditis mentioning influenza vaccine as suspect collected w/n Vaccine Adverse Event Reporting System (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 immune checkpoint inhibitors 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 immune checkpoint inhibitors in cancer patients negligible from clinical and epidemiological standpoints • Findings support cardiovascular safety of influenza vaccination, which remains strongly recommended in cancer patients
Valachis, 2021[11]	retrospective ***(Level IV)***	All patients previously not treated w checkpoint inhibitors and who	303	Patients considered vaccinated if they had received influenza vaccination during	• Most common type of malignancy was melanoma (47.8%) followed by NSCL cancer (31.0%)

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		received monotherapy w PD-1 or PD-L1 blocker		treatment w checkpoint inhibitor or up to 60 days prior to treatment initiation (n=236)	• 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 immune-related AE grade was comparable b/n vaccinated and non-vaccinated group (p=0.85) • Study indicates survival improves w influenza vaccination while not increasing risk for side effects in cancer patients treated w checkpoint inhibitors
Gogenur, 2020[12]	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 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)	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) • 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, there was 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
Li, 2021[13]	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 hospitalisations 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

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					• Older age, no insurance, more comorbidities, lung cancer and haematological 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
Collins, 2020[14]	retrospective ***(Level IV)***	Hospitalized immunocompromised (IC) adults with influenza	3633	Details re. vaccination type not reported; influenza season under study was 2011-2015	• Among 35 348 adults, 3633 (10%) were IC; cancer (44%), nonsteroid immunosuppressive therapy (44%), and HIV (18%) most common • IC patients more likely than non-IC patients to have received influenza vaccination (53% vs 46%; *P*<0.001), and ~85% of both groups received antivirals • In multivariable analysis, IC adults had higher mortality (adjusted odds ratio [aOR], 1.46; 95% CI, 1.20-1.76) • Intensive care more likely among IC 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-IC patients in those age groups • IC 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 nonimmunocompromised 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 IC adults hospitalized w- influenza
Ayoola, 2020[15]	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 weeks were 35%, 30% and 22.5% to H1N1, H3N2 and B/Bris strains, respectively. No new cases of late seroconversion at 6 weeks or 24 weeks • Seroconversion rate at 3 weeks were 72.5%, 65% and 40%, respectively, to H1N1, H3N2 and B/Bris. Seroconversion rate at 24 weeks to H1N1, H3N2 and B/Bris were 40%, 52.5% and 17.5%, respectively. • Patients on various solid tumour treatments achieve sero-protection rate congruent with general population. Sero-protection haemagglutination-inhibiting antibody titres not sustained at 24 weeks postvaccination
Bayle, 2020[16]	prospective ***(Level III)***	Advanced cancer patients receiving single-agent immune checkpoint inhibitor targeting PD-1 NSCLC, n=25 Urothelial carcinoma, n=5	30	Single, standard dose of French National Health authorities-approved, subcutaneous influenza vaccine 7 (±2) days after last administration of immune checkpoint inhibitor	• Median time under immune checkpoint inhibitor treatment at time of vaccination was 3 months (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, with 7 patients (23%) showing seroconversion factor >1000

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		Males 83%, median age 63 yrs. (range: 47-78)] Nivolumab n=7, Pembrolizumab n=8) or PD-L1 (atezolizumab n=15)			• Influenza infection not documented among 30 vaccinated patients for 6 months following vaccination • No grade 4-5 immune-related adverse event observed, and 15 patients (50%) developed grade 1-3 immune-related adverse event for 6 months following influenza vaccination shot, proportion similar to that observed in patients receiving single-agent immune checkpoint inhibitors • Data suggest that influenza vaccination in patients under immune checkpoint inhibitors is safe and effective
Bersanelli, 2020[17]	retrospective ***(Level IV)***	Patients with primary advanced cancer and any systemic treatment with 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) • Within elderly patients, flu vaccine was main variable for relative OS advantage (p=0.05) • Receiving flu vaccine and/or developing influenza syndrome related to better OS within INVIDIa population
Failing, 2020[18]	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	Within 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 with unspecified type	• Vaccinated group significantly older (*P*=0.002) and received more cycles of pembrolizumab (*P*=0.006) • Incidence of any grade immune-related adverse events in vaccinated group trended toward being lower (25.7% vs 40.2%; *P*=0.07) compared with nonvaccinated group • Influenza vaccination independently associated with fewer immune-related adverse events, with OR 0.4 (95% CI, 0.2 to 0.9; *P*=0.03) in multivariable analyses • Vaccinated group less likely to have immune-related adverse events compared with nonvaccinated group (24.7% vs 34.4% at 12 months; *P*=0.05), with death as competing risk • Median immune-related adverse event-free duration in vaccinated group longer than nonvaccinated group (not reached vs 28 months; *P*=0.037) • Influenza vaccination in patients with cancer receiving immune checkpoint inhibitor therapy not associated with increased immune-related adverse events
Joona, 2020[19]	prospective ***(Level III)***	1. Female patients >18 yrs. with stage I, II, or operable stage III HER2+ breast cancer treated with	20	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 was observed for either H1N1 (100% in both groups) or B strain (78.9% vs. 89.2%, p value=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 weeks, p value <0.001;

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		trastuzumab in adjuvant setting 2. Healthy controls	37		baseline vs 12 weeks, p value=0.042) and healthy controls (baseline vs 4 weeks, p value <0.001; baseline vs 12 weeks, p value=0.012) • Immunogenicity analysis for H1N1 strain showed significant differences among 3 time points in both trastuzumab-treated patients (baseline vs 4 weeks, p value<0.001; baseline vs 12 weeks, p value=0.039) and healthy controls (baseline vs 4 weeks, p value<0.001; baseline vs 12 weeks, p value=0.014) • Adverse events in the trastuzumab-treated group were uncommon and mild with only 1 serious adverse event not related to vaccination • Current data support recommendation to offer influenza vaccination in breast cancer patients treated with subcutaneous trastuzumab
Kang, 2020[20]	prospective ***(Level III)***	Patients with cancer receiving: 1. anti–PD-1 immune checkpoint inhibitors (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 the 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 immune checkpoint inhibitor 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 were more frequent in immune checkpoint inhibitor 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 were greater in immune checkpoint inhibitor group • Immune checkpoint inhibitor administration strongly associated with adequate cell-mediated immunogenicity response for both CD4+ and CD8+ T cells (P=0.003) • Cell-mediated immunogenicity responses following influenza vaccination stronger in immune checkpoint inhibitor group than in cytotoxic CT group • Influenza vaccination should be strongly recommended in patients with cancer receiving immune checkpoint inhibitors
Keam, 2020[21] *(*no access to supplementary data to report exact numbers in results section)*	prospective ***(Level III)***	Patients >20 yrs. with cancer who received: 1. Immune checkpoint inhibitors 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 the 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 concomitantly on day 1 of chemotherapeutic cycle	• Most common cancer was lung cancer in both groups. Nivolumab and pembrolizumab were most commonly used immune checkpoint inhibitors • Seroprotection and seroconversion rates significantly higher in immune checkpoint inhibitor group than in cytotoxic CT group for all strains, except for H1N1 strain • Postvaccination geometric mean titers for hemagglutination inhibition antibodies significantly higher in immune checkpoint inhibitor group for all strains, after adjusting for prevaccination geometric mean titers • Proportions of cumulative strains detected in seroprotection or seroconversion tests significantly higher in immune checkpoint inhibitor than in cytotoxic CT group • Found independent association between immune checkpoint inhibitor and number of strains protected against, after adjusting for age > 60 yrs., cancer type, and baseline hemagglutination inhibition antibody titers • In all subgroup analyses, immune checkpoint inhibitor group showed tendency toward higher seroprotection rates than cytotoxic CT group • Among 47 and 92 patients in immune checkpoint inhibitor and cytotoxic CT groups, respectively, rates of conventional adverse events comparable

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					• Among patients receiving immune checkpoint inhibitors, identified 4 (9%) immune-related adverse events during follow-up period, all grade 1 • Results support annual influenza vaccinations for cancer patients receiving immune checkpoint inhibitors
Bersanelli, 2019[22]	systematic review ***(Level I)***	Advanced cancer patients receiving immune checkpoint inhibitors	1993	Any study reporting or considering use of influenza vaccination during therapy with immune checkpoint inhibitors was 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 immune checkpoint inhibitor therapy not specifically proven • Only few retrospective studies currently available in literature on topic • Only based on pharmacological characteristics of immune checkpoint inhibitor antibodies, influenza vaccination has been considered as potentially safe in patients treated with cancer immunotherapy • No prospective studies assessing clinical efficacy of influenza vaccination during immunotherapy with immune checkpoint inhibitor in cancer patients • Scarce and controversial evidence about influenza vaccination during anticancer therapy with immune checkpoint inhibitor confirms need of more robust data on safety of vaccine during immunotherapy and, consequently, on its advisability in a population where its usefulness has not yet specifically been proven
Blanchette, 2019[23]	retrospective test-negative ***(Level IV)***	Adult patients with 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 with cancer who underwent influenza testing, with 4,320 test-positive cases (16%) and 11,783 (45%) vaccinated • Mean age 70 yrs., 52% were male, mean time since diagnosis 6 yrs., 69% had solid tumor malignancies, and 23% received active CT • Vaccine effectiveness against laboratory-confirmed influenza was 21% (95% CI, 15% to 26%), and vaccine effectiveness against laboratory-confirmed influenza hospitalization was 20% (95% CI, 13% to 26%) • For patients with solid tumor malignancies, vaccine effectiveness was 25% (95% CI, 18% to 31%), compared with 8% (95% CI, –5% to 19%) for patients with hematologic malignancies (*P*=0.015) • Active CT usage did not significantly affect vaccine effectiveness, especially among patients with solid tumor cancer • Results support recommendations for influenza vaccination for patients with cancer. Strategies to optimize influenza prevention among patients with cancer are warranted
Chong, 2019[24]	retrospective review ***(Level IV)***	Patients with solid tumours (lung=165, melanoma=71, other=134) treated with immune checkpoint inhibitors	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 within 65 days of cancer therapy	• N=75 (20%) experienced a new onset immune related AE (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 immune related AEs: endocrine (28% of all AEs) pneumonitis (25%), colitis (13%), transaminitis (12%) • Proportion of patients who experienced any immune related AE was highest among those treated with ipilimumab+nivolumab (25/82, 30%) • For patients on an anti-PD1 agent only, the overall immune related AE rate was 17% (38/227)

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					• The proportion of patients who experienced serious (grade 3 or 4) immune related AEs was higher among those treated with ipilimumab+nivolumab (11/82, 13%) vs. those treated with anti-PD1 agents alone (15/227, 6.6%)
Gwynn, 2019[25]	prospective case series ***(Level V)***	Patients with solid tumours treated with immune checkpoint inhibitors	24	2017-18 inactivated quadrivalent influenza vaccine	• N=7 patients with 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[26]	retrospective case control ***(Level IV)***	Patients with solid tumours or Hodgkin lymphoma treated with immune checkpoint inhibitors: 1. Cases: developed myocarditis 2. Controls: no myocarditis	 101 201	Various	• Influenza vaccination was administered to 25% of the cases vs. 40% of the 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 a major adverse cardiac event during the median 175-day follow-up; 24% vaccinated vs. 59% unvaccinated cases, p=0.002)
Bersanelli, 2018[27]	multicentre retrospective cohort ***(Level IV)***	Patients with advanced cancer (NSCLC=103, RCC=112, melanoma=55, other=30) treated with immune checkpoint inhibitors 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 the NSCLC subgroup, incidence of influenza=27% vaccinated vs. 17% unvaccinated (OR=1.81; 95% CI 0.67–4.86, p=0.29) • In the elderly subgroup (>71 years, 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 were seen in response rate, disease control rate, or time to treatment failure between vaccinated vs. unvaccinated patients or between patients developing vs. not developing influenza
Strowd, 2018[28]	prospective cohort ***(Level III)***	CNS tumours (high-grade glioma=23, CNS lymphoma=3, meningioma =1) treated with RT, CT, or glucocorticoids	27	2013-14 inactivated quadrivalent high-dose influenza vaccine	• No grade III-IV toxicity reported • Seroconversion rates for the A/H1N1=65%, A/H3N2=69%, and B strains=50%, and all were 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-months post-vaccination • Seroconversion was universally poor in patients with post-treatment lymphopenia
Wijn, 2018[29]	retrospective cohort ***(Level IV)***	Patients with NSCLC treated with 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 the rates of discontinuation, death, clinical deterioration or tumour response between groups

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Bitterman, 2018[30]	systematic review ***(Level I)***	6 studies conducted between 2013-2017 including adults with hematologic and solid tumours	2275	Various	• Observational data suggest lower mortality and infection-related outcomes with vaccination • The evidence, although weak, shows that the benefits overweigh the potential risks when vaccinating adults with cancer against influenza. • There is no conclusive evidence regarding the use of adjuvanted versus non-adjuvanted influenza vaccine in this population
Waqar, 2018[31]	prospective cohort ***(Level III)***	Patients with non-hematologic malignancies receiving CT: 1. Vaccinated on day of CT 2. Vaccinated 1 week before CT	8 10	2011-12 trivalent inactivated influenza vaccine	• Seroconversion against H1N1, H3N2, and B strains was 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 the 3 influenza strains were not significantly different between the 2 groups • All of the patients (8/8) vaccinated in group 1 demonstrated seroprotection to at least 1 strain, compared with 60% of patients in group 2 • Seroprotection rates were 50% for all 3 strains in group 1, and they were 20% (2/10), 40% (4/10), and 50% (5/10) for strains H1N1, H3N2, and B, respectively in group 2
Läubli, 2018[32]	prospective trial ***(Level III)***	1. Patients with lung cancer receiving immune checkpoint inhibitors 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 immune-related adverse events (irAEs) was 52.2% with a median time to occurrence of 3.2 months after vaccination • 6/23 patients (26.1%) showed severe grade 3 or 4 immune-related adverse events, including N=2 colitis, N=2 encephalitis, N=1 peripheral neuropathy, N=1 pneumonitis; other adverse events included N=3 rash, N=3 arthritis, and N=1 hypothyroidism
Branagan, 2017[33]	prospective trial ***(Level III)***	Patients with 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 the 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 the second dose (67% to 96%, $p < 0.001$) and seroconversion against all three strains increased from 39% to 55% after second vaccination ($p=0.02$) • Rate of laboratory-confirmed influenza infection=6%
Nakashima, 2017[34]	prospective cohort ***(Level III)***	Patients with 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 with lung cancer receiving platinum doublet treatment exhibited lower seroprotection rates than those receiving a single agent
Keam, 2017[35]	randomized controlled trial ***(Level II)***	Breast & lung cancer patients receiving CT: 1. Vaccinated on day 1 of CT cycle	43	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%, $p=0.306$

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
		2. Vaccinated on day 11 of CT cycle	54		• Adverse events day 1 group vs. day 11 group = 13% vs. 32%, p=0.040
La Torre, 2016[36]	systematic review and meta-analysis ***(Level I)***	22 studies conducted between 1993-2016 including adult and pediatric patients with 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[37]	multicentre prospective trial ***(Level III)***	Patients with 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 the first vaccination	• Proportion of patients with protective titres against all 3 viral strains increased from 3 to 27% following vaccination (p< 0.01) • 79 patients received a second vaccination; the proportion of those with • protective titres against the individual strains increased by 10% (H1N1), 8% (H3N2), and 3% (B) from the first vaccination • No serious adverse events observed
Sun, 2016[38]	prospective cohort ***(Level III)***	CLL patients treated with 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 within 6 months of immunization
Jamshed, 2016[39]	randomized controlled trial ***(Level II)***	cancer patients <65 years of age receiving chemotherapy: 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 adverse events reported • seroconversion rates for all 3 influenza antigens and post-vaccination GMTs for H3N2 and B strains were significantly improved in patients receiving high-dose vs. standard-dose
Berglund, 2014[40]	prospective trial ***(Level III)***	cancer outpatients receiving ongoing treatments with chemotherapy, monoclonal antibodies, tyrosine kinase inhibitors or corticosteroids	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 with rituximab did not respond to immunization • For the patients not treated with rituximab: ○ 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[41]	prospective cohort ***(Level III)***	CNS tumours (GBM = 21, high-grade gliomas = 5, low-grade gliomas = 6, primary CNS lymphoma = 6) treated with 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

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Vinograd, 2013[42]	prospective non-intervention trial ***(Level III)***	patients with solid tumours receiving CT and hematologic patients with 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[43]	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 was predictive of responders
Lagler, 2012[44]	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 with solid tumours who were 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[45]	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 vs. 134, p< 0.05), were lower for pts with hematologic malignancies vs. health controls • Patients not receiving CT had seroprotection and GMTs similar to 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[46]	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) • Active CT (p=0.01), lymphoma (p=0.03), rituximab (p<0.001), and steroid treatment (p=0.02) associated with lesser antibody responses in cancer pts
Xu, 2012[47]	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 between groups •
Rousseau, 2012[48]	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 adverse events were mild to moderate

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Puthillath, 2011[49]	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 with regards to CT administration
Miraglia, 2011[50]	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[51]	prospective controlled trial	1. Lymphoma treated with rituximab ± CT 2. Healthy controls	67 51	Monovalent adjuvanted influenza A (H1N1) vaccine x 1 dose	• Seroprotection: 0% lymphoma vs. 82% controls
Monkman, 2011[52]	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 with lymphoid vs. non-lymphoid malignancies
de Lavallade, 2011[53]	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) • 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[54]	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 adverse events related to the vaccine
Mackay, 2011[55]	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=.11) • Seroconversion: 45% vs. 19% (solid vs. hematologic; p=.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 pts • Immunization was well tolerated
Sasson, 2011[56]	prospective cohort	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 the three strains of vaccine

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
	(Level III)				• 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[57]	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 the global quantitative recovery of T-cell and B-cell subsets or in global T-cell and B-cell function
Chadha, 2011[58]	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 with response (p=.045) and all upper quartile 25-D3 patients responded (p=.034) •
Mulder, 2011[59]	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[60]	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 with fludarabine (European immunogenic criteria not met); CD27(+) memory B-cells reduced among patients vs. controls
Meerveld-Eggink, 2011[61]	randomized controlled trial ***(Level II)***	1. Breast cancer – FEC chemotherapy 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 that there was a broad serum antibody response to the influenza virus vaccine in patients treated with chemotherapy for breast cancer
Avetisyan, 2008[62]	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 with the community and are more exposed to infection by circulating respiratory viruses • *Authors recommend the influenza immunization 3 months or longer after allo-SCT, as long as there is no GVHD or ongoing immunosuppression*

Ljungman, 2005[63]	open, randomized ***(Level II)***	Hematologic malignancies (N=59 receiving active CT against malignancy)	36
			34
				1. one-dose vaccine
				2. two-doses vaccine
				
				minimum of 1 week between immunization and the 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 with myeloproliferative disorders responded better to H1N1 vs. multiple myeloma patients (p=.002) and patients with lymphoma also responded better than patients with multiple myeloma (p<.001)
					• Trend for better responses in patients with less intensive CT
					• *Authors recommend immunization of family members and hospital staff*

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

Machado, 2005[64]	prospective cohort ***(Level III)***	Hematologic malignancies:
		1. < 6 months post-BMT, not eligible for immunization
		2. ≥ 6 months 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 were vaccinated, and vaccine efficacy was 80%
					• 12/24 (50%) unvaccinated in group 2 developed influenza
					• Multivariate analysis:
					  ○ Seasonal exposure and conditioning regimens independently associated with increased risk for influenza
					  ○ influenza vaccine and steroid therapy showed a protective role
					• Gender, BMT type, underlying disease and GVHD not associated with risk of influenza infection

Earle, 2003[65]	retrospective cohort ***(Level IV)***	1. Stage IV colorectal cancer patients who received seasonal influenza vaccine 2. Stage IV colorectal cancer patients who were not immunized	626 951	Seasonal influenza vaccine	• SEER database and the 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 with an HR for death of 0.88 (95%CI, 0.77-0.99) • *68% of patients who were immunized received their immunization through a primary care physician, yet oncologists are often these patients' most consistent medical contacts. As a result, it is critical that oncologists actively provide routine influenza immunization to their patients with advanced cancer as part of delivering comprehensive, high-quality cancer care*
Nordoy, 2002[66]	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%) were serologically protected against 2 of the 3 flu strains • A higher proportion of the patients with solid tumours (81%) than lymphoma (38%) achieved protection • *Age, duration of CT, and curative vs. palliative treatment did not influence immunization response*

Table 2: Summary of Published Literature on Influenza Immunization in Pediatric Patients with Cancer, January 2000 – August 2022

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Doganis, 2018[67]	prospective cohort ***(Level III)***	Patients with leukemia (48), lymphoma (5), and solid tumours (22); median age = 8.8 years	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 with a higher post-vaccination seroprotective titer: ALC >1000/mm3 for H1N1, age >9 years, or solid tumors for H3N2 and B strains • Variables that correlated with a significantly higher seroconversion rate: solid tumours and prevaccination HAI≥40 Variables that correlated significantly with higher post-vaccination GMTs: GMTs before vaccination, high ALC at the vaccination time, and solid tumours for H1N1; GMTs before vaccination and solid tumours were also significant factors for higher post-vaccination GMTs for H3N2 and influenza B
Sykes, 2017[68]	retrospective cohort ***(Level IV)***	patients with acute leukemia treated on the TOTALXVI protocol; median age = 6 years	498	2011-12, 2012-13, and 2013-14 inactivated trivalent seasonal vaccines	• 354/498 were vaccinated (71.1%) and 98 were given a 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[69]	retrospective cohort ***(Level IV)***	Children treated for ALL between 2000-2012; median age = 4.1 years	60	Booster dose of inactivated conjugated Haemophilus influenza B given at least 3 months after the end of CT	• Seroprotection rate at the end of CT = 20% • Seroprotection rate after booster dose administered = 92% During the previous influenza season, 18 mothers (40.0%), 19 fathers (42.2%), and 16 siblings (35.6%) had received the seasonal influenza vaccine
Choi, 2016[70]	prospective cohort ***(Level III)***	Patients receiving CT for solid tumours (76) and hematologic malignancies (183) were studied over 2 years	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 was higher in seroresponders than nonresponders (854 cells/mm^3 vs. 602 cells/mm^3, p< 0.036) • Patients with an ALC <1,000 cells/mm^3 at time of vaccination were 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[71]	randomized open-label trial ***(Level II)***	Children and young adults (3-21 years) with 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[72]	prospective cohort ***(Level III)***	Children with hematologic and solid tumours aged 6 months-18 years receiving or within 4 weeks 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 with solid tumors significantly more likely to serorespond to each vaccine strain compared to children with hematologic malignancies ○ H3N2: OR=7.39, 95% CI 2.42–22.53, p< 0.01 ○ 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

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					Children with 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 with hematological malignancies
Ottóffy G, 2014[73]	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 with 2009 seasonal influenza vaccine x 1 dose	• Pre- and post-immunization seroprotective rates were 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 were 22%, 37%, and 22%, respectively, and 30% for the pandemic H1N1 vaccine • Determinants of responsiveness were 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[74]	randomized, double-blind, phase I safety trial ***(Level II)***	ALL (80% on maintenance therapy)	34 16	1. High-dose TIV (60 µg) Standard-dose TIV (15 µg)	• no significant differences reported in local or systemic symptoms • No severe adverse events attributed to vaccine No significant differences in immune response between the high- and standard-dose TIV groups
Dotan, 2014[75]	prospective cohort ***(Level III)***	Patients with leukemia (16), lymphoma (10), neuroblastoma (4), and other malignancies (10) admitted to hospital with 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%) were influenza A/H1N1 positive • 2/13 (15%) H1N1-positive episodes were previously immunized versus 14/44 (32%) H1N1-negative episodes (p=0.3) • No sig demographic differences between groups with and without influenza A/H1N1 infection; no difference in proportion who received CT in the influenza A/H1N1-positive group vs. the 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 with fever and URI symptoms vs. 24/41 (59%) episodes in unvaccinated children (p=0.38)
Goossen, 2013[76]	meta-analysis (Cochrane Review) ***(Level I)***	Pediatric malignancies	770	• 9 controlled clinical trials and 1 RCT were included in the review • In 5 studies, immune responses to influenza vaccine were compared in 272 children on CT with 166 children not on CT • In 4 studies, responses to influenza vaccine were assessed in 236 children on CT compared with responses in 142 healthy children • Immune responses in children receiving CT were 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%) • Adverse events included mild local reactions and low-grade fever; no persistent or life-threatening effects reported *Authors concluded that although pediatric oncology patients receiving CT are able to generate an immune response to the influenza vaccine, it is unclear whether this immune response protects them from influenza infection or its complications*	
Leahy, 2013[77]	prospective cohort ***(Level III)***	ALL	45	Patients received 2 doses of the inactivated split-virion AS03-adjuvanted vaccine. Serological response measured before each vaccine dose (days 0 & 28) and 3 months after the second dose.	• Pre and post titres were available from 45 children after 1 vaccine dose and 39 children after 2 doses. The seroconversion rates were 11.1% after 1 dose and 25.6% after 2 doses. • Significantly higher (p= 0.01) seroconversion rate among children who received the 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 the seroconversion rate. Children who received the adult dose demonstrated significantly greater magnitude of serological response after 1 dose (p = 0.04) and 2 doses (p = 0.001).

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Mavinkurve-Groothuis, 2013[78]	prospective cohort ***(Level III)***	Children with hematologic malignancies (20) or solid tumours (11) treated with CT or within 6 months after the end of CT	31	Inactivated split-virion preparation of the A/California/07/2009(H1N1)v-like strain x 2 doses (3-week interval)	• No sig. difference in the immunization response between patients with hematologic cancer vs. solid tumours. • Sig. difference in the absolute lymphocyte count prior to the first immunization between patients with protective vs. no protective response (p= 0.012). • Absolute lymphocyte counts for above the lower normal limits (LNL) for age were seen in 13/28 patients (46%). In 12/13 patients (92%), a protective response to immunization was seen. In the 15 patients with absolute lymphocyte counts below the LNL for age, only 5 (33%) had a protective response to immunization (p=0.002). No protective immunization response observed in patients with $CD4^+$ T cell count less than 200/mm^3.
Karras, 2012[79]	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 month	• Seroprotection: no significant differences at 8 weeks 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 weeks 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) None of the patients vaccinated <1 yr. from SCT showed seroconversion to the H3N2 virus vs. 39% of patients vaccinated ≥1 yr. (p=0.001); similarly, only 6% and 8% of patients in the <1 yr. group seroconverted to H1N1 and influenza B, respectively, whereas 64% (p=0.001) and 39% (p=0.003) seroconverted in the ≥1 yr. group
Kersun, 2012[80]	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 with a 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[81]	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[82]	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[83]	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 the last dose • Seroconversion: achieved in 48% of hematology patients and 50% of solid tumour patients after the last dose No significant differences in seroconversion or seroprotection rates between patients who received one dose versus two doses
Carr, 2011[84]	randomized trial ***(Level II)***	Solid and hematological, receiving or received CT	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)

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		or RT within last 3 months			• 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 adverse events reported (febrile illness and seizure)
Yen, 2011[85]	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 without pre-vaccine seroprotective titer than those with (50% vs. 15%, p=.07) and greater in those with 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[86]	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[87]	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[88]	case series ***(Level V)***	Patients with solid tumours aged 1-18 years on CT or within 6 months of completing CT	45	2 doses of the trivalent split vaccine 1 month apart	• Fourfold rise in the percentage of post-immunization antibody titers was detected for: H1N1 (84.4%), H3N2 (77.8%), and influenza B (60%) • Stratification of patients on active CT versus within 6 months 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 were 86 to 97%
Matsuzaki, 2005[89]	controlled clinical trial ***(Level IV)***	Pediatric malignancies	44	2 doses of influenza vaccine 2-4 weeks apart	• Response rates: H1N1 65%; H3N2 40%; influenza B: 46% • Patients on CT showed a significantly lower response than those who were immunized after completing CT; protection titers were: H1N1=42% vs. 90% (p=.006), H3N2=25% vs. 83% (p=.019) • For influenza B, patients with low IgG showed a lower response rate than those with higher IgG (29% vs. 61%, p=.040) • Multivariate analysis showed that factors associated with low immune response were: 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[90]	controlled clinical trial ***(Level IV)***	Pediatric patients with solid tumours or lymphoma actively receiving CT or who were within 6 months of completing CT	66	1 or 2 doses of influenza vaccine, in autumn 2001 and/or 2002	• Following immunization: ○ 25/64 patients (38%) were protected against all three viruses, representing a full response ○ Protective responses to one or two viral strains were 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 were: ○ H1N1: 29% (95% CI 17–42%, p<.0001) ○ H3N2: 22% (95% CI 10–33%, p=.0002)

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					○ Influenza B: 43% (95% CI 29–57%, p< .0001) • N= 27 patients transfused with blood and/or platelets during the study: ○ N=10 (38%) showed no response ○ N=6 (23%) showed a protective response to 1-2 viral subunits ○ N=10 (38%) were protected against all 3 viruses • in multivariate analysis, lymphopenia was associated with improved response for H1N1 (OR=11.4, 95% CI 1.11–117.37; p= .041), though the authors caution that the number of patients with lymphopenia was small • There was no significant difference in response rates among children on treatment and off treatment and by intensity of CT regimen
Porter, 2004[91]	controlled clinical trial ***(Level IV)***	1. ALL in 1st remission, maintenance CT, completed last delayed intensification at least 4 weeks 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 month apart) for previously unimmunized children or those <9 yrs. of age	Although post-immunization geometric mean titres were lower in group 1 versus group 2 children for the H1N1 antigen (p<.001), H3N2 antigen (p=.03), and influenza B antigen (p=.003), at least 60% of children with ALL had at least a 4-fold increase in HAI titres to each of the influenza antigens
Hsieh, 2002[92]	controlled clinical trial ***(Level IV)***	1. Pts with ALL in maintenance stage; received 6-mercaptopurine + methotrexate, and reinduction with vincristine + prednisolone 2. Pts with 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 weeks after the 2nd immunization • Seroconversion rates after 2 doses of vaccine were 57.1 to 84.6% and seroresponse rates were between 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 were comparable in group 1 and group 2 children • Antibody response in group 1 children who received reinduction CT suggests that the therapy did not impair seroresponse rates

Abbreviations: *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; 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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Appendix A: Search Strategy

Database	Date	Search Strategy	Results
PubMed	Aug. 26, 2022	1. carcinoma[MeSH Terms] 2. neoplasm[MeSH Terms] 3. cancer[Title/Abstract] 4. tumor[Title/Abstract] 5. tumour[Title/Abstract] 6. ((((tumour[Title/Abstract]) OR (tumor[Title/Abstract])) OR (cancer[Title/Abstract])) OR (neoplasm[MeSH Terms])) OR (carcinoma[MeSH Terms]) 7. influenza A virus[MeSH Terms] 8. influenza B virus[MeSH Terms] 9. influenza, human[MeSH Terms] 10. influenza[Title/Abstract] 11. (((influenza[Title/Abstract]) OR (influenza, human[MeSH Terms])) OR (influenza B virus[MeSH Terms])) OR (influenza A virus[MeSH Terms]) 12. immunization[MeSH Terms] 13. vaccination[MeSH Terms] 14. immun*[Title/Abstract] 15. vaccin*[Title/Abstract] 16. (((vaccin*[Title/Abstract]) OR (immun*[Title/Abstract])) OR (vaccination[MeSH Terms])) OR (immunization[MeSH Terms]) 17. (((((vaccin*[Title/Abstract]) OR (immun*[Title/Abstract])) OR (vaccination[MeSH Terms])) OR (immunization[MeSH Terms])) AND ((((influenza[Title/Abstract]) OR (influenza, human[MeSH Terms])) OR (influenza B virus[MeSH Terms])) OR (influenza A virus[MeSH Terms]))) AND (((((tumour[Title/Abstract]) OR (tumor[Title/Abstract])) OR (cancer[Title/Abstract])) OR (neoplasm[MeSH Terms])) OR (carcinoma[MeSH Terms])) ***Limit 17 to Humans, English, from 2021/8/1 to present ***Excluded case reports, duplicates from 2021, covid 19, non-cancer or non-human subjects (i.e., mice, in vitro), vaccine uptake and equity, vaccine design	712,272 3,723,199 2,033,334 1,339,093 233,293 4,602,569 48,112 4,554 55,595 109,909 119,912 200,362 102,321 2,688,037 386,195 2,903,841 2,466 111 2
Medline	Aug. 30, 2021	1. exp Neoplasms/ 2. exp Carcinoma/ 3. “cancer”.ab. 4. “cancer”.ti. 5. “tumor”.ab. 6. “tumor”.ti. 7. “tumour”.ab.	3527011 676487 1571007 1066463 1152332 287691 202957

		8. “tumour”.ti. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp Influenza A virus/ 11. “influenza A virus”.ab. 12. “influenza A virus”.ti. 13. exp Influenza B virus/ 14. “influenza B virus/”.ab. 15. “influenza B virus/”.ti. 16. 10 or 11 or 12 or 13 or 14 or 15 17. exp Immunization 18. “immunization”.ab. 19. “immunization”.ti. 20. 17 or 18 or 19 21. 9 and 16 and 20 22. limit 21 to (english language and yr=”2019-Current”) 23. 16 or 20 24. 9 and 23 25. limit 24 to (english language and yr=”2019-Current”) 26. exp Influenza, Human/ 27. 9 and 26 28. influenza.ab. 29. influenza.ti. 30. 26 or 28 or 29 31. 9 and 20 and 30 32. limit 31 to (english language and yr=”2019-Current”) 33. exp Vaccination/ 34. vaccination.ab. 35. vaccination.ti. 36. 20 or 33 or 34 or 35 37. 9 and 30 and 36 38. limit 37 to (english language and yr=”2019-Current”) 39. from 38 keep 9-11, 14, 16-18, 27, 34, 47…	49414 4347994 46154 9578 5301 4434 1267 544 50159 186537 82119 28230 238163 151 8 282296 32697 2398 52739 1074 81488 73664 111233 607 51 92179 117742 55890 307202 1025 116 33
Medline	Aug. 5, 2020	1. exp Neoplasms/ 2. exp Carcinoma/ 3. “cancer”.ab. 4. “cancer”.ti. 5. “tumor”.ab. 6. “tumor”.ti. 7. “tumour”.ab. 8. “tumour”.ti. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. exp Influenza A virus/ 11. “influenza A virus”.ab.	3347460 643670 1434014 980631 1069164 269966 193066 47469 4102770 43712 8915

		12. “influenza A virus”.ti.	4994
		13. exp Influenza B virus/	4186
		14. “influenza B virus/”.ab.	1206
		15. “influenza B virus/”.ti.	521
		16. 10 or 11 or 12 or 13 or 14 or 15	47547
		17. exp Immunization/	175364
		18. “immunization”.ab.	78391
		19. “immunization”.ti.	27396
		20. 17 or 18 or 19	225284
		21. 9 and 16 and 20	144
		22. limit 21 to (english language and yr=”2019-Current”)	5
		23. 16 or 20	267147
		24. 9 and 23	30361
		25. limit 24 to (english language and yr=”2019-Current”)	1601
		26. exp Influenza, Human/	49244
		27. 9 and 26	997
		28. influenza.ab.	75288
		29. influenza.ti.	70113
		30. 26 or 28 or 29	104266
		31. 9 and 20 and 30	564
		32. limit 31 to (english language and yr=”2019-Current”)	37
		33. exp Vaccination/	84871
		34. vaccination.ab.	106362
		35. vaccination.ti.	50621
		36. 20 or 33 or 34 or 35	287549
		37. 9 and 30 and 36	940
		38. limit 37 to (english language and yr=”2019-Current”)	84
		39. from 38 keep 1, 4, 7, 10-11, 19, 27-29…	21

Appendix B: 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