Received: 10 November 2020 | Accepted: 23 November 2020

DOI: 10.1111/petr.14025

MINIREVIEW

WILEY

Preparing for the 2020—2021 influenza season

Annabelle de St. Maurice[1] | Rachel Martin-Blais[1] | Natasha Halasa[2]

[1]Division of Pediatric Infectious Diseases, Department of Pediatrics, UCLA David Geffen School of Medicine, Los Angeles, CA, USA

[2]Division of Pediatric Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical Center, Los Angeles, CA, USA

Correspondence
Annabelle de St. Maurice, Division of Pediatric Infectious Diseases, Department of Pediatrics, UCLA David Geffen School of Medicine, Los Angeles, CA, USA.
Email: adestmaurice@mednet.ucla.edu

Abstract

The COVID-19 pandemic has altered health seeking behaviors and has increased attention to non-pharmaceutical interventions that reduce the risk of transmission of respiratory viruses including SARS-CoV-2 and influenza. While the potential impact of the COVID-19 pandemic on influenza is not fully known, in the Southern hemisphere influenza infection rates appear to be very low. Influenza vaccine efficacy for 2019–2020 season was comparable to prior season and influenza vaccine recommendations for pediatric immunizations remain similar to prior years. Influenza treatments continue to include neuraminidase inhibitors as well as baloxavir for treatment and in some instances prophylaxis.

KEYWORDS
covid, influenza, sars cov 2, vaccine

1 | 2019–2020 INFLUENZA SEASON NORTHERN AND SOUTHERN HEMISPHERE

The 2019–2020 influenza season was marked by decreased influenza transmission during the COVID-19 pandemic likely resulting from differences in health seeking behaviors, physical distancing, mask wearing, and attention to personal hygiene.[1] In the Northern hemisphere, influenza activity started to decrease by mid to late February 2020.[2] Looking at the United States specifically, influenza activity had begun to increase in November 2019 and started to sharply decrease by March 2019. In fact, a 98% decrease in influenza activity was noted between the time periods of September 29, 2019–February 29, 2020 and March 1-May 16, 2020. Inter-seasonal influenza circulation from May 17 to August 8, 2020 was also at historic lows.

In the Southern hemisphere from April to July 2020, influenza rates remained low in Australia Chile, and South Africa. In these three countries, only 51 of 83 307 specimens (0.06%) tested positive for influenza from April to July 2020 compared to 24 512 of 178 690 (13.7%) positive specimens detected from April to July 2017–2019.[2]

Influenza activities remained low in the Northern hemisphere and Southern hemisphere in September and October 2020.[1] In tropical Northern Africa, South America, Caribbean, and Central American countries there have been no influenza detections reported.

In tropical Africa, only Cote D'Ivoire and Mali reported cases of influenza. In Europe, influenza activity is at inter-seasonal levels, however, Ireland has seen increased influenza like illness activity likely related to SARS-CoV-2 circulation. East Asia has experienced baseline inter-seasonal levels of influenza like illness, however, in Southern, Central and Western Asia there were no or few influenza detections. In Cambodia and Lao PDR influenza like illness related to influenza A(H3N2) continued to increase.

From September 2020 to October 2020, the National Influenza Centres and national influenza laboratories submitted 81 257 respiratory specimens to the WHO FluNet; of these 172 specimens were positive for influenza.[1] Influenza A accounted for the majority of cases worldwide, with 108 (63%) of cases typed as influenza A and 64 (37%) typed as influenza B. Of the influenza A cases, 6% were influenza A(H1N1)pdm09 and 94% were influenza A(H3N2). Of the B viruses, 8% belonged to the B-Yamagata lineage and 92% to the B-Victoria lineage.

While inter-seasonal influenza rates remain low and influenza activity was very low in the Southern hemisphere during the peak of their flu season, it is difficult to extrapolate this to the Northern hemisphere since COVID-19 mitigation measures vary across countries.

Abbreviations: an NAI, intranasal laninamivir; HSCT, hematopoietic stem cell transplant; LAIV, Live attenuated influenza vaccine; NA, neuraminidase; NAIs, neuraminidase inhibitors; PA, polymerase acidic; SA, sialic acid; SOT, solid organ transplant recipients.

For example, in Australia a mandatory 14-day hotel quarantine was imposed for all returned travelers in March, later accompanied by lockdowns and bans on gatherings.[2] In Chile, curfews and lockdowns and mandatory masking were used as strategies to mitigate the spread of COVID-19. As regions in the United States, Europe, and Southeast Asia are experiencing increases in COVID-19 cases[3] it is unclear whether or not these regions will also have a mild flu season.

2 | SARS-CoV-2 AND INFLUENZA

Because SARS-CoV-2 (the virus that causes COVID-19) and influenza have similar modes of transmission and clinical presentation, differentiating between the two diseases is difficult. Epidemiologic data suggest that SARS-CoV-2 is more infectious than influenza.[4] Both SARS-CoV-2 and influenza can cause respiratory disease and gastrointestinal illness. A recent study found that more children with COVID-19 had evidence of fever, diarrhea or vomiting, headache, body ache, or chest tightness than children with influenza at the time of diagnosis.[5] Yet, one differentiating feature of COVID-19 is the loss of sense of taste or smell.

Because of the similar clinical presentations of these respiratory viruses, it is important for providers to test for both influenza and SARS-CoV-2 infection when evaluating patients with influenza-like illness during the influenza season. Co-infection with influenza and SARS-CoV-2 is not infrequent in pediatric patients[6]; therefore, patients with a positive influenza test should also be tested for SARS-CoV-2. Healthcare facilities should invest in combination platforms that diagnose both influenza and SARS-CoV-2 this season.[7]

3 | ZOONOTIC INFLUENZA VIRUSES

Zoonotic avian influenza cases in birds and humans are reported to the WHO in order to rapidly identify strains with pandemic potential. Several strains have been monitored by WHO including H5, H7, H9N2. From February 2020 to October 2020, no human cases of influenza A(H5) were identified, however, cases have been identified in wild birds and poultry.[8] Influenza A (H7) has been detected in poultry in the United States and Australia but no human cases have been identified. Five human cases of H9N2 have been identified in China, all were in children less than eight, and all had mild illness. Candidate H5 and H7 vaccines are currently being developed as a preventive measure.

Swine flu strains include influenza (H1)v and influenza A(H3N2). Human influenza A(H1)v cases have been documented Germany and Brazil from February 2020 to October 2020.[8] A single influenza A(H3N2) case was noted in the United States. Candidate swine flu vaccines are also undergoing evaluation.

4 | Flu VACCINE EFFICACY

Flu vaccine efficacy is monitored by a variety of surveillance systems both nationally and globally. Efficacy can be determined by studying rates of infection in vaccinated individuals compared to unvaccinated individuals and can be stratified by populations at risk.[9] Additional estimates of vaccine efficacy can be obtained by studying mortality or hospitalization and comparing immunized to non-immunized individuals. These estimates can be obtained through active (e.g. public health research collaboratives) or passive surveillance (e.g. mandatory reporting).

According to the 2019–2020 CDC data, preliminary flu vaccine efficacy in the United States during the 2019–2020 influenza season was estimated to be 39% for all influenza A or B types).[10] Vaccine efficacy was 31% for influenza A(H1N1)pdm09 viruses and 44% for influenza B/Victoria viruses. In Europe, vaccine estimates were estimated to range from 29 to 61% in the primary care setting against all influenza types.[11]

Data for the 2020 flu season in Australia has demonstrated a 44% influenza A(H1N1)pdm09 isolate match and 65% influenza A(H3N2) match.[12] Of the few influenza B isolates all were antigenically similar to the corresponding vaccine component. Although vaccine efficacy in Australia has not been estimated, it appears as though the circulating influenza strains are similar to those contained in the vaccine.

5 | Flu VACCINE ADMINISTRATION UPDATES

Recommendations for flu vaccine composition for the Southern and Northern hemisphere by the WHO can be found in Table 1a,b. The WHO SAGE working group recommends that governments work to ensure that influenza vaccine supply is sustainable given potential shortages associated with the COVID-19 pandemic.[13] Influenza vaccines that have been prequalified for use by different regulatory agencies can be found on the WHO website at: https://extranet.who.int/pqvdata/Browse.aspx?nav=3 along with the national regulatory agency that has approved the vaccine.

Two influenza vaccines were recently licensed for use in adults ≥65 years of age in the United States.[14] These two vaccines, Fluzone High-Dose Quadrivalent vaccine and Fluad Quadrivalent vaccine, effectively replace the high-dose trivalent vaccine. Immunogenecity and safety of these quadrivalent vaccines were compared to trivalent formulations and were found to be similar. FluAd has also been approved by the European Union for use in persons 65 years of age and older.[15]

LAIV use varies globally. LAIV remains an option in the United States for individuals age 2 through 49 years[14] and in the European Union for individuals 2 through 17 years of age.[15] In Canada, LAIV is licensed for use in individuals 2–59 years of age.[16] Live attenuated flu vaccine has not been licensed in Australia.[17] In low and middle income countries in Asia and Africa, the efficacy of LAIV has been studied with variable results.[18]

Numerous public health and transplant organizations recommend against live attenuated influenza vaccination in SOT and HSCT recipients due to the theoretical risk of infection, although the virus is cold-adapted and should not replicate at body temperature.[19-21]

TABLE 1 WHO recommendations for composition of Egg-based (a) Cell or recombinant-based (b) Seasonal Influenza Vaccine 2020–2021 Northern Hemisphere and 2021 Southern Hemisphere[a,b]

	Northern Hemisphere	Southern Hemisphere
(a)		
Trivalent Influenza Vaccine (TIV)	A/Guangdong-Maonan/SWL 1536/2019 (H1N1) pdm09-like virus	A/Victoria/2570/2019 (H1N1)pdm09-like virus
	A/Hong Kong/2671/2019 (H3N2)-like virus	A/Hong Kong/2671/2019 (H3N2)-like virus
	B/Washington/02/2019 (B/Victoria lineage)-like virus	B/Washington/02/2019 (B/Victoria lineage)-like virus
Quadrivalent Influenza Vaccine (QIV)[c]	B/Phuket/3073/2013-like virus (B/Yamagata lineage)-like virus	B/Phuket/3073/2013-like virus (B/Yamagata lineage)-like virus
(b)		
Trivalent Influenza Vaccine (TIV)	A/Hawaii/70/2019 (H1N1) pdm09-like virus	A/Wisconsin/588/2019 (H1N1) pdm09-like
	A/Hong Kong/45/2019 (H3N2)-like virus	A/Hong Kong/2671/2019 (H3N2)-like virus
	B/Washington/02/2019 (B/Victoria lineage)-like virus	B/Washington/02/2019 (B/Victoria lineage)-like virus
Quadrivalent Influenza Vaccine (QIV)[c]	B/Phuket/3073/2013-like virus (B/Yamagata lineage)-like virus	B/Phuket/3073/2013-like virus (B/Yamagata lineage)-like virus

[a]Modified from: https://www.who.int/influenza/vaccines/virus/recommendations/2021_south/en/. Accessed October 29, 2020.

[b]Modified from: https://www.who.int/influenza/vaccines/virus/recommendations/2020-21_north/en/. Accessed October 29, 2020.

[c]includes same three antigens of TIV plus additional B antigen.

The American Society for Transplantation recommends that if a live influenza vaccine is inadvertently given to a SOT recipient, antiviral therapy and revaccination with an inactivated vaccine can be considered.[21] The AST states that live attenuated vaccine can be given prior to transplantation as long as the transplant is occurring two weeks or more following vaccination.

Annual influenza vaccines are recommended annually at the beginning of the influenza season. However, optimal timing of vaccine administration post-transplant in SOT and HSCT recipients continues to be studied, but most experts recommend HSCT recipients receive inactivated influenza vaccine at least 3–6 months after HSCT and 2–6 months after SOT.[21-23] There is insufficient evidence to routinely recommend administering multiple influenza vaccine doses during a single influenza season or for administering high dose influenza vaccine to either SOT or HSCT recipients; however these continue to be studied.[24,25] However, the European Conference on Infections in Leukemia suggests that a second dose of influenza vaccine may be considered in individuals with graft versus host disease or lymphopenia or during an influenza outbreak if individuals are immunized less than six months after transplant.[19]

6 | INFLUENZA TREATMENT UPDATES

Children with influenza-like symptoms who are at high risk of complications from influenza infection (such as those who have received previous transplants) should all be offered antiviral medications as soon as the illness is suspected—before virologic confirmation.[26] While the greatest benefit will likely be achieved if (NAIs) are given within 48 h of onset of illness, there is likely still some benefit to administration ≥48 h after illness begins—particularly for immunocompromised patients who may have prolonged viral shedding—and the AAP recommends that this be offered.[26]

For many years, the adamantane class of drugs was the only available treatment for influenza, and then only for influenza A (influenza B viruses being intrinsically resistant).[27] Amantadine and rimantadine, the primary agents of this class, act by inhibiting the M2 protein ion channel, preventing uncoating and viral assembly.[27] These drugs were relatively effective for susceptible strains of influenza A; however, resistance-conferring mutations occurred in large proportions of patients taking adamantane medications for ≥5 days. Unfortunately, a large proportion of influenza A viruses since 2005 have been found to be resistant to the adamantanes, and so the use of these drugs are no longer recommended.[27,28]

Fortunately, the number and types of medications available for treatment of influenza have been expanding (Table 2). The adamantanes have been largely replaced by newer drugs targeting different parts of the viral replication process, which have been developed using advancements in rational drug design, such as identifying active compounds based on a target enzyme's structure.[29]

NAIs such as oseltamivir, zanamivir, and peramivir act as SA analogues, preventing viral budding by competitively inhibiting the NA-mediated cleavage of SA that results in viral particle release.[30] Each is given by a different route (oral, inhaled, and intravenous, respectively), and is approved for use in a different age group. Two of them, oseltamivir and zanamivir, may be given for both treatment and chemoprophylaxis. It is worth noting that several studies have shown reduced efficacy of neuraminidase inhibitors in children with asthma, although they are still recommended as treatment for patients with a history of asthma.[26]

Oseltamivir is by far the most commonly used of the NAIs, and AAP guidelines identify oseltamivir as the first-line therapy for

TABLE 2 Drugs for Treatment of Influenza 2020–2021

Drug Name	Ages	Restrictions/Contraindications	Dose		Route	Duration	Common Adverse Effects
Oseltamivir (Tamiflu®)	≥14 days[a]		**Infants <12 months**		Oral	5 days[c]	Nausea/vomiting, hallucinations and post-marketing concerns for neuropsychiatric effects
			Age	**Dose**			
			Preterm	Dependent on post-menstrual age			
			Term, 0–8 months	3 mg/kg BID			
			9–11 months	3–3.5 mg/kg BID[b]			
			Children ≥12 months				
			Weight	**Dose**			
			≤15 kg	30 mg BID			
			>15–23 kg	45 mg BID			
			>23–40 kg	60 mg BID			
			>40 kg	75 mg BID			
Zanamivir (Relenza®)	≥7 years	Not recommended for patients with asthma/lung disease	10 mg (two 5-mg administrations) BID		Inhaled	5 days[c]	Bronchospasm
Peramivir (Rapivab®)	≥2 years		12 mg/kg over 15–30 min; maximum dose 600 mg		Intravenous	1 dose[c]	Diarrhea
Baloxavir marboxil (Xofluza®)	≥12 years	No data on hospitalized patients; minimal data on immunocompromised and pregnant individuals[8]	40-<80 kg: 40 mg ≥80 kg: 80 mg		Oral	1 dose	Gastrointestinal distress (vomiting/diarrhea)
Amantadine		Not recommended for 2020–2021 season due to likely resistance	N/A		Oral	N/A	Neuropsychiatric effects, gastrointestinal distress (nausea/vomiting)
Rimantadine		Not recommended for 2020–2021 season due to likely resistance	N/A		Oral	N/A	Neuropsychiatric effects, gastrointestinal distress (nausea/vomiting)

Note: Sources: AAP,[26] CDC,[33] IDSA[40]

[a]FDA-approved from 14 days of age; however, CDC and AAP recommend use from birth.

[b]FDA and CDC-approved dosing is 3 mg/kg; however, AAP recommends 3.5 mg/kg/dose.

[c]Longer durations may be considered for immunocompromised individuals and/or patients requiring hospitalization for severe lower respiratory infection.

influenza infection in children.[26] If oseltamivir solution is not available, then capsules may be opened and mixed with simple syrup or sugar-free solution in the pharmacy or at home to form an easily administrable liquid formulation.[26,31] In general, oseltamivir is well tolerated; the only adverse effect that exceeded those of placebo in trials was gastrointestinal distress and vomiting.[26] Post-marketing reports of neuropsychiatric effects (including fatal self-injury) in children from Japan have led to significant concern and FDA labeling changes. A clear link to oseltamivir as the cause has not been established, and some speculate that the neurologic effects may be due to influenza infection itself; nonetheless, caution is recommended in pediatric patients.[26,32]

Baloxavir marboxil is a cap-dependent endonuclease inhibitor which impairs the influenza virus's ability to "cap-snatch" (and thus transcribe viral mRNA) by interfering with the virus's PA protein. It was FDA-approved for children ≥12 years of age in late 2018, and has few adverse effects. Its use in immunocompromised individuals is currently not recommended by the CDC, due to lack of data in this population[33]; however, early reports of its use for these patients are promising.[34,35] In previously healthy individuals, baloxavir appeared to be as effective as oseltamivir after a single dose, and decreased duration of viral shedding significantly when compared with oseltamivir.[36] Recent studies of its use in children <12 years of age have demonstrated comparable efficacy to oseltamivir.[37]

Several trials have looked into the use of high-titer intravenous immunoglobulin (IVIg) or anti-influenza plasma for treatment of patients with severe influenza disease; however, these have not resulted in clear patient benefit, and thus are not recommended for management of influenza.[38,39] Likewise, corticosteroids are not recommended for treatment of influenza, due to lack of evidence of benefit and possible evidence of harm.[40]

7 | ANTIVIRAL RESISTANCE

There have been reports of resistance to antiviral medications, such as the NAIs and baloxavir, even during the course of normal treatment. Post-transplant patients—and those who received HSCTs in particular—are at higher risk than the general public for developing resistant virus due to limited immune response to infection. However, after one dose of baloxavir, resistance has developed in nearly a quarter of healthy children. Testing for NAI resistance mutations can be considered in patients who develop influenza despite chemoprophylaxis, immunocompromised or severely ill patients with ongoing illness and persistently positive RT-PCR / viral cultures after 7–10 days of therapy, and patients who received suboptimal NAI doses.[40] However, clinical worsening may not necessarily be due to drug failure, as adverse effects of immunosuppressive medications may also mimic worsening infection in these patients.[40] Those who present with particularly severe disease or sudden decompensation after initial improvement should be evaluated and treated for bacterial superinfection. Fungal superinfection should also be considered, particularly in immunocompromised individuals.[40]

The most common NAI resistance mutation—marked by a H275Y substitution in the N1-containing influenza A viruses' NA gene—leads to decreased susceptibility to oseltamivir and peramivir, but maintains susceptibility to zanamivir. Because of this, patients suspected of having developed oseltamivir/peramivir resistance should be transitioned to zanamivir if no contraindication is present; however, as other mutations may confer resistance to all NAIs, zanamivir may also be found to be ineffective.[40] Thankfully, NAI and PAI resistance remains generally low, with worldwide estimates of 0.8% and 0.08%, respectively, for the 2017–2018 influenza season.[41] Combination therapy may prove useful for combatting resistant disease and/or decreasing emergence of resistance for high-risk individuals, but is largely based on theory and small studies and/or case reports, and some analyses have documented a lack of differences in clinical outcomes with this approach.[42-46]

8 | NON-US-APPROVED DRUGS/DRUGS IN DEVELOPMENT

Several anti-influenza drugs have been developed and licensed for use in Japan, including (an NAI) and favipiravir, a RNA-dependent RNA polymerase inhibitor that has received attention for possible uses in influenza and SARS-CoV-2. The latter's erratic drug levels and variable efficacy have kept it from being widely approved for the treatment of influenza to date, and the Japanese government recommends its use only for influenza infections where other drugs are not effective.[42,47] Pimodivir is a novel type of anti-RNA-dependent RNA polymerase inhibitor that is under current clinical trials, with some promising results to date.[48]

9 | CHEMOPROPHYLAXIS

Previous randomized, controlled trials of NAIs have shown that oseltamivir and zanamivir may prevent infections in individuals living in a household with a person who has been diagnosed with a laboratory-confirmed case of influenza. Prophylaxis with peramivir has not been studied; however, a very recent study of baloxavir prophylaxis suggests that it may be effective for this purpose, although resistance does quickly emerge.[26,49] It is recommended that chemoprophylaxis begin within 48 h of initial exposure; post-exposure prophylaxis is not recommended after 48 h due to risk of promoting resistance, and the need for early initiation of treatment should instead be emphasized if more than two days have elapsed since contact with an infected individual.[40] Chemoprophylaxis options are listed in Table 3. Doses for chemoprophylaxis are lower than treatment doses, and so any concern for true disease should prompt immediate increase to therapeutic doses.[26]

Chemoprophylaxis should never be used as a substitute for vaccination—only as an adjunct measure—since immunization has significant benefits for individuals and the population as a whole, including decreased severity of illness if it does occur.[50,51] It should be

TABLE 3 Drugs for Chemoprophylaxis of Influenza, 2020–2021

Drug Name	Ages	Restrictions	Chemoprophylaxis Dose	Route	Duration	Common Adverse Effects
Oseltamivir (Tamiflu®)	≥3 months (can be given from birth if judged critically necessary)[17]		**Infants 3–12 months** **Age** / **Dose** Preterm, 3–12 months: No data Term, 3–8 months: 3 mg/kg daily 9–11 months: 3–3.5 mg/kg daily[b] **Children ≥12 months** **Weight** / **Dose** ≤15 kg: 30 mg daily >15–23 kg: 45 mg daily >23–40 kg: 60 mg daily >40 kg: 75 mg daily	Oral	7 days[a]	Nausea/vomiting, hallucinations and post-marketing concerns for neuropsychiatric effects
Zanamivir (Relenza®)	≥5 years	Not recommended for patients with asthma/lung disease	10 mg (two 5-mg administrations) daily	Inhaled	7 days[a]	Bronchospasm
Baloxavir marboxil (Xofluza®)	≥12 years	No data on hospitalized patients[8]	40 - <80 kg: 40 mg ≥80 kg: 80 mg	Oral	1 dose	Gastrointestinal distress (vomiting/diarrhea)

[a]Consider chemoprophylaxis for the duration of the influenza season for HSCT recipients in the first 6–12 months after transplant, lung transplant recipients, and transplant recipients who are unable to be vaccinated.

[b]FDA and CDC-approved dosing is 3 mg/kg; however, AAP recommends 3.5 mg/kg/dose.

noted that all pediatric transplant societies recognize that influenza vaccination is important to prevent severe disease, and recommend its prioritization as soon as possible in the influenza season.[21,52] Providers should note that use of antiviral medication at the time of LAIV (but not IIV) administration may impair response.[26] This is less likely to be a concern for pediatric transplant patients, as live virus vaccines are contraindicated for the majority of transplant recipients.

For adults and children ≥3 months of age with very high risk of influenza-related complications and for whom vaccination is contraindicated or likely to be ineffective, chemoprophylaxis for the entire influenza season may be considered. Short-term chemoprophylaxis can also be given to high-risk individuals while awaiting response after vaccine administration, or to their close contacts if chemoprophylaxis of the immunocompromised individual is contraindicated and influenza is circulating in the community.[40]

10 | CONCLUSIONS

The impact of COVID-19 mitigation measures on influenza cases in the Northern hemisphere during the latter part of the 2019–2020 season was significant. Influenza cases were also markedly decreased in the Southern hemisphere during the 2020 season. The 2020–2021 influenza season in the Northern hemisphere will be difficult to predict given increases in COVID-19 cases. Efforts to increase immunization rates among transplant recipients are particularly important this year to avoid the possibility of co-infection with influenza and SARS-CoV-2. Treatment options for influenza exist but should be given as early as possible to be most effective.

AUTHOR CONTRIBUTIONS

Dr. de St. Maurice, Dr. Martin-Blais, and Dr. Halasa both reviewed, critically evaluated, and summarized the literature. Dr. Halasa, Dr. Martin-Blais, and Dr. de St. Maurice were involved in drafting and reviewing the paper and have approved the final version.

DISCLOSURES

Dr. Halasa receives grant support from Quidel and Sanofi; vaccine donation and HAI/MN testing support from Sanofi; and speaker compensation from an educational grant support by Genentech.

ORCID

Annabelle de St. Maurice https://orcid.org/0000-0001-7368-7403

REFERENCES

1. WHO. Influenza Updated 379. https://www.who.int/influenza/surveillance_monitoring/updates/2020_10_26_surveillance_update_379.pdf?ua=1. 2020. Accessed November 2, 2020.
2. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic–United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(37):1305-1309.
3. WHO. Weekly Operational update on COVID-19. 2020.
4. Petersen E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis*. 2020;20(9):e238-e244.
5. Song X, Delaney M, Shah RK, Campos JM, Wessel DL, DeBiasi RL. Comparison of clinical features of COVID-19 vs seasonal influenza A and B in US Children. *JAMA Netw Open*. 2020;3(9):e2020495.
6. Wu Q, Xing Y, Shi L, et al. Coinfection and other clinical characteristics of COVID-19 in children. *Pediatrics*. 2020;146(1):e20200961.
7. Balakrishnan VS. In preparation for a COVID-19-influenza double epidemic. *Lancet Microbe*. 2020;1(5):e199.
8. WHO. Antigenic and genetic characteristics of zoonotic influenza A viruses and development of candidate vaccine viruses for pandemic preparedness 2020. https://www.who.int/influenza/vaccines/virus/202009_zoonotic_vaccinevirusupdate.pdf?ua=1. Accessed November 2, 2020.
9. Minodier L, Blanchon T, Souty C, et al. Influenza vaccine effectiveness: best practice and current limitations of the screening method and their implications for the clinic. *Expert Rev Vaccines*. 2014;13(8):1039-1048.
10. Centers for Disease Control and Prevention. US Flu VE Data for 2019-2020. https://www.cdc.gov/flu/vaccines-work/2019-2020.html. 2020. Accessed November 2, 2020.
11. European Centres for Disease Control and Prevention. Seasonal influenza 2019-2020. https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2019_influenza-seasonal.pdf. 2020.
12. Australian Government Department of Publica Health. Australian Influenza Surveillance Report. November 15, 2020.
13. WHO. WHO SAGE Seasonal influenza vaccination recommendations during the COVID-19 Pandemic 2020. September 21, 2020.
14. Grohskopf LA, Alyanak E, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices–United States, 2020–21 influenza season. *MMWR Recomm Rep*. 2020;69(8):1-24.
15. European Centres for Disease Control and Prevention Types of seasonal influenza vaccine. https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/types-of-seasonal-influenza-vaccine. 2020. Accessed November 2, 2020.
16. Public Health Association of Canada. Canadian immunization guide chapter on influenza and statement on seasonal influenza vaccine for 2020–2021. 2020.
17. Australian Government Department of Health. Influenza (flu). https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/influenza-flu. 2020. Accessed November 2, 2020.
18. Ortiz JR, Neuzil KM. Influenza Immunization in Low- and Middle-Income Countries: Preparing for Next-Generation Influenza Vaccines. *J Infect Dis*. 2019;219(Supplement_1):S97-S106.
19. Cordonnier C, Einarsdottir S, Cesaro S, et al. Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European conference on infections in leukaemia (ECIL 7). *Lancet Infect Dis*. 2019;19(6):e200-e212. https://doi.org/10.1016/S1473-3099(18)30600-5
20. Public Health Association of Canada. Canadian Immunization Guide. https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html. 2020. Updated 2020. Accessed November 2, 2020.
21. Danziger-Isakov L, Kumar D. Practice AICo. Vaccination of solid organ transplant candidates and recipients: guidelines from the American society of transplantation infectious diseases community of practice. *Clin Transplant*. 2019;33(9):e13563.
22. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44-e100.
23. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation

recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.
24. Hirzel C, Kumar D. Influenza vaccine strategies for solid organ transplant recipients. *Curr Opin Infect Dis*. 2018;31(4):309-315.
25. Haddadin Z, Krueger K, Thomas LD, Overton ET, Ison M, Halasa N. Alternative strategies of posttransplant influenza vaccination in adult solid organ transplant recipients. *Am J Transplant*. 2020;21(3):938-949.
26. Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2019–2020. *Pediatrics*. 2019;144(4):e20192478.
27. Harrison GJ. *Antiviral Agents*. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases* (8th edn). Elsevier; 2019:2417-2436.
28. *Pinkbook | Influenza | Epidemiology of Vaccine Preventable Diseases*. CDC. https://www.cdc.gov/vaccines/pubs/pinkbook/flu.html#virus. Accessed November 2, 2020.
29. McCullers JA. *Influenza Viruses*. *Feigin and Cherry's Textbook of Pediatric Infectious Diseases* (8th edn). Elsevier; 2019:1729-1745.
30. McAuley JL, Gilbertson BP, Trifkovic S, Brown LE, McKimm-Breschkin JL. Influenza virus neuraminidase structure and functions. *Front Microbiol*. 2019;10:39.
31. *Opening and Mixing Oseltamivir Capsules with Liquids if Child Cannot Swallow Capsules | Centers for Disease Control and Prevention*; 2020. https://www.cdc.gov/flu/highrisk/mixing-oseltamivir-qa.htm. Accessed November 3, 2020.
32. Han N, Oh JM, Kim I-W. Assessment of adverse events related to anti-influenza neuraminidase inhibitors using the FDA adverse event reporting system and online patient reviews. *Sci Rep*. 2020;10(1):3116.
33. Centers for Disease Control and Prevention. What You Should Know about Flu Antiviral Drugs. 2020. https://www.cdc.gov/flu/treatment/whatyoushould.htm. Accessed November 3, 2020.
34. Harada N, Shibata W, Koh H, et al. Successful treatment with baloxavir marboxil of a patient with peramivir-resistant influenza A/H3N2 with a dual E119D/R292K substitution after allogeneic hematopoietic cell transplantation: a case report. *BMC Infect Dis*. 2020;20(1):478.
35. Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2020;20(10):1204-1214.
36. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med*. 2018;379(10):913-923.
37. Baker J, Block SL, Matharu B, et al. Baloxavir marboxil single-dose treatment in influenza-infected children: a randomized, double-blind, active controlled phase 3 safety and efficacy trial (miniSTONE-2). *Pediatr Infect Dis J*. 2020;39(8):700-705.
38. Davey RT, Fernández-Cruz E, Markowitz N, et al. Anti-influenza hyperimmune intravenous immunoglobulin for adults with influenza A or B infection (FLU-IVIG): a double-blind, randomised, placebo-controlled trial. *Lancet Respir Med*. 2019;7(11):951-963.
39. Beigel JH, Aga E, Elie-Turenne M-C, et al. Anti-influenza immune plasma for the treatment of patients with severe influenza A: a randomised, double-blind, phase 3 trial. *Lancet Respir Med*. 2019;7(11):941-950.
40. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the infectious diseases society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):e1-e47.
41. Takashita E, Daniels RS, Fujisaki S, et al. Global update on the susceptibilities of human influenza viruses to neuraminidase inhibitors and the cap-dependent endonuclease inhibitor baloxavir, 2017–2018. *Antiviral Res*. 2020;175:104718.
42. Lumby CK, Zhao L, Oporto M, et al. Favipiravir and Zanamivir cleared infection with influenza B in a severely immunocompromised child. *Clin Infect Dis*. 2020;71(7):e191-e194.
43. Wang Y, Fan G, Salam A, et al. Comparative effectiveness of combined Favipiravir and Oseltamivir therapy versus Oseltamivir monotherapy in critically III patients with influenza virus infection. *J Infect Dis*. 2020;221(10):1688-1698.
44. Checkmahomed L, Padey B, Pizzorno A, et al. Combinations of Baloxavir acid and other inhibitors against seasonal influenza A viruses. *Viruses*. 2020;12(10):1139. https://doi.org/10.3390/v12101139
45. Beigel JH, Bao Y, Beeler J, et al. Oseltamivir, amantadine, and ribavirin combination antiviral therapy versus oseltamivir monotherapy for the treatment of influenza: a multicentre, double-blind, randomised phase 2 trial. *Lancet Infect Dis*. 2017;17(12):1255-1265.
46. Mifsud EJ, Hayden FG, Hurt AC. Antivirals targeting the polymerase complex of influenza viruses. *Antiviral Res*. 2019;169:104545.
47. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacol Ther*. 2020;209:107512.
48. Finberg RW, Lanno R, Anderson D, et al. Phase 2b study of Pimodivir (JNJ-63623872) as monotherapy or in combination with oseltamivir for treatment of acute uncomplicated seasonal influenza A: TOPAZ Trial. *J Infect Dis*. 2019;219(7):1026-1034.
49. Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir Marboxil for prophylaxis against influenza in household contacts. *N Engl J Med*. 2020;383(4):309-320.
50. Centers for Disease Control and Prevention. Key facts about seasonal Flu vaccine. 2020.
51. Piñana JL, Pérez A, Montoro J, et al. Clinical effectiveness of influenza vaccination after allogeneic hematopoietic stem cell transplantation: A cross-sectional, prospective, observational study. *Clin Infect Dis*. 2019;68(11):1894-1903.
52. Ryan AL, Wadia UD, Jacoby P, et al. Immunogenicity of the inactivated influenza vaccine in children who have undergone allogeneic haematopoietic stem cell transplant. *Bone Marrow Transplant*. 2020;55(4):773-779.

How to cite this article: de St. Maurice A, Martin-Blais R, Halasa N. Preparing for the 2020—2021 influenza season. *Pediatr Transplant*. 2021;25:e14025. https://doi.org/10.1111/petr.14025