Guidance on Use of Antiviral Agents for the 2019-20 Influenza Season

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ABSTRACT

The use of antiviral agents for seasonal influenza is influenced by several factors, including but not limited to the available agents, antiviral drug resistance, the nature of high-risk groups and vaccine effectiveness. With respect to the latter, influenza vaccine is recommended annually to reduce the influenza-associated disease burden, particularly among those at high risk of serious influenza complications, including the elderly and individuals with certain conditions, such as: pregnancy, immunosuppression, diabetes mellitus, and cardiovascular, respiratory, hepatic and renal diseases(1). Surveillance signals suggest the potential for low vaccine effectiveness (VE) for some components of the 2019-20 seasonal influenza vaccine in Canada. Given this concern, the role of antivirals may be more important, notably for high-risk groups. This and related issues are addressed in this document. Additional details on influenza antiviral drug recommendations can be found in the AMMI Canada Foundation Document(2).

The use of antiviral medications complements other strategies aimed at reducing severe outcomes from influenza illness. Other strategies include vaccination, infection control, social distancing and hygiene measures. The importance of antiviral agents is enhanced during seasons when vaccine effectiveness (VE) might be sub-optimal.

Available Antiviral Agents: The antiviral agents that are currently available and recommended for use in Canada for seasonal influenza for the 2019-20 season are the neuraminidase inhibitors, oral **oseltamivir phosphate** (available as a generic version or under the trade name Tamiflu®) and inhaled **zanamivir** (Relenza®). Intravenous **peramivir** (a parenteral only neuraminidase inhibitor; Rapivab®) is approved but is not currently marketed in Canada.

For dosage regimens and further details, please refer to the AMMI Canada Foundation Document(2).

Baloxavir Marboxil (Xofluza®) has a mechanism of action that is different from the neuraminidase inhibitors. It is a selective inhibitor of influenza cap-dependent endonuclease, but is not currently available for use in Canada.

Amantadine, an M2 inhibitor, is available in Canada but should not be used for treatment or prophylaxis because of widespread resistance among circulating influenza A strains and intrinsic lack of activity against influenza B.

Antiviral Resistance to Neuraminidase Inhibitors: Rates of antiviral resistance and reduced susceptibility to the neuraminidase inhibitors remain low. However, it is important that these rates are monitored to detect changes as they occur. Current Canadian drug resistance surveillance data can be found at FluWatch(3). In addition, clinicians should be aware of groups at an increased risk of developing resistance during treatment(4), such as immunocompromised individuals(5) and young children(6).

Target Populations: For the 2019-20 seasonal influenza season, the target populations for the use of antivirals remain unchanged from the previous season. In cases of documented or suspected influenza infection, antiviral (oseltamivir or zanamivir) treatment should be considered for adults and children at high risk of serious influenza complications or in individuals with progressive, severe, or complicated illness, *regardless of whether they received the 2019-20 seasonal influenza vaccine*(1, 7). Otherwise healthy patients with relatively mild influenza are not likely to benefit from antiviral therapy initiated more than 48 hours after illness onset.

Treatment should be initiated as rapidly as possible after onset of influenza-like illness (ILI) typically including sudden onset of fever and cough and other respiratory or systemic symptoms(8). Of note, fever may not be prominent in elderly adults. Antiviral treatment of high-risk individuals should not await diagnostic test results. Effectiveness is reduced when treatment is initiated >48 hours after illness onset but should still be considered if the illness is progressive, severe, or complicated, regardless of previous health status, or if the individual belongs to a group at high risk for severe disease.

Antiviral Chemoprophylaxis: Early therapy is generally preferred over seasonal pre-exposure prophylaxis in the community setting for individuals at high risk of serious influenza complications. An early treatment strategy may involve counselling together with arrangements to have medication on hand for an ILI that is likely due to influenza.

Post-exposure antiviral prophylaxis may be appropriate for persons at very high risk of influenza complications after significant exposure to an infectious contact, e.g., living in the same household, ideally no later than 48 hours after exposure(7). Early presumptive treatment is preferred if >48 hours has elapsed since exposure.

Antiviral prophylaxis for the control of influenza outbreaks in healthcare facilities may, at the discretion of the local Medical Health Officer, include staff in addition to patients or residents. Where considered, such offer to staff/patients should be regardless of whether they received the 2019-20 seasonal influenza vaccine.

Anticipated 2019-20 VE: Influenza VE — defined as the reduction in risk of influenza-associated disease in vaccinated compared to unvaccinated people under real-world conditions — varies from year to year. A systematic review of VE studies from 2004 to 2015 reported pooled VEs of 67% (95% CI, 29 – 85), 33% (95% CI, 26 – 39), and 61% (95% CI, 57 – 65) for influenza A/H1N1, A/H3N2 and influenza B, respectively(9).

Anticipating circulating influenza virus strains for annual vaccine preparation remains a challenge. This is of particular importance for the A(H3N2) subtype of the influenza virus, which has been associated with a higher burden of disease relative to A(H1N1) viruses and influenza B viruses, particularly in older adults. Based on currently available data, vaccine mismatch for two of the influenza vaccine components may be anticipated for the 2019-20 season, including the A(H3N2) subtype and the B(Victoria) lineage strains. Influenza A(H1N1) viruses continue to diversify but so far remain antigenically similar to the 2019-20 vaccine strain, as are B(Yamagata) lineage viruses.

Influenza A(H3N2) viruses belonging to the 3C.2a1b genetic sub-group predominated during the 2018-19 season in the northern hemisphere and continued to predominate and diversify in regions of the southern hemisphere, notably Australia, during their 2019 influenza season. North American data indicate that sub-group 3C.2a1b viruses remain prominent among the low-level A(H3N2) detections thus far in the autumn 2019 in both Canada and the United States (US). Whether this pattern will continue through the 2019-20 influenza season is difficult to predict(10, 11).

After a delayed recommendation, the A(H3N2) vaccine component for the upcoming 2019-20 Northern hemisphere season was updated to A/Kansas/14/2017 (H3N2)-like virus, a clade 3C.3a virus(12). Clade 3C.3a viruses are considered antigenically distinct from sub-group 3C.2a1b viruses and therefore there is concern about possible vaccine mismatch for the 2019-20 season on that basis(10, 12-14).

In addition, influenza B viruses from the Victoria lineage have been diversifying and demonstrating a relatively greater contribution compared to prior seasons when Yamagata lineage viruses predominated. Currently, predominant Victoria lineage viruses have a triple deletion in the hemagglutinin protein. The 2019-20 trivalent and quadrivalent influenza vaccines contain B/Colorado/06/2017-like virus, a Victoria lineage strain instead bearing a double deletion in the hemagglutinin protein. Triple versus double deletion Victoria lineage viruses are considered antigenically distinct, and therefore there is also concern about suboptimal vaccine protection for the 2019-20 season for that component (10, 12-14). However, the immuno-epidemiology underpinning influenza B susceptibility in the population is complex. This includes observations that children and young adults may be relatively more affected during B/Victoria compared to B/Yamagata lineage epidemics (15), but also the potential for some cross-lineage protection (16). Ongoing surveillance and VE monitoring are therefore important.

Summary: Most healthy people fully recover from influenza illness without medical intervention or antiviral treatment. However, given the potential for suboptimal VE this season, antiviral therapy may be of particular importance in the management of individuals with suspected influenza illness despite documentation of having received the 2019-20 influenza vaccine.

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