Update on Influenza Antiviral Drug Treatment and Prophylaxis for the 2015-2016 Influenza Season

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Influenza Antiviral Drug Treatment and Prophylaxis for the 2015-2016 Influenza Season: Update

Readers are referred to the AMMI Foundation Document on antiviral drugs for influenza, and to the 2014-2015 supplements for treatment and prophylaxis of influenza illness in 1. Acute care facilities, and 2. Long-term care facilities. [1-3]

Insights from the 2014-15 influenza season:

During the 2014-15 season, the influenza vaccine provided negligible protection against the dominant influenza A(H3N2) clade 3C.2a epidemic strain as measured in Canada[4-6] and elsewhere globally.[7,8] Multiple (10-12) amino acid differences between the vaccine and circulating virus located at key antigenic sites of the hemagglutinin protein likely played a role in reducing vaccine protection.[4,9-11] In February 2015, the WHO recommended a change from the A/Texas/50/2012-like (clade 3C.1) strain used as H3N2 component for the 2014-15 vaccine to an A/Switzerland/9715293/2013-like (clade 3C.3a) strain for the 2015-16 vaccine.[12]

Emerging findings during the 2015-16 influenza season:

Although influenza activity remains at low levels to date (November 21, 2015), influenza A(H3N2) viruses have again emerged as dominant early in the season. Since September 1, 2015, 365 (91%) influenza A viruses and 37 (9%) influenza B viruses have been detected and of the 244 influenza A viruses subtyped, 163 (86%) have been H3N2 [13]. The clade 3C.2a strain that caused the 2014-15 epidemic continues to predominate among H3N2 detections. In British Columbia (BC), Canada, of approximately 80 H3N2 detections between mid-June and early-November 2015 sequenced by the BC Centre for Disease Control (BCCDC) Public Health Laboratory, all were clade 3C.2a, including sporadic, cruise ship and facility outbreak specimens (verbal communication, D Skowronski, BCCDC). Despite vaccine reformulation, dominant clade 3C.2a viruses still bear multiple (10-12) amino acid differences at key antigenic sites compared to the 2015-16 updated (clade 3C.3a) vaccine component, (verbal communication, D Skowronski, BCCDC).

As also observed last season, a minority (<5%) of H3N2 viruses (1/27) submitted to Canada's National Microbiology Laboratory (NML) could be successfully characterized by hemagglutination inhibition assay (HIA) so far this season.[17] Although considered antigenically-similar to a cell-passaged version of the chosen 2015-16 vaccine strain, it is unclear how representative that may be of the remaining 95% of H3N2 viruses that could not be antigenically characterized. Recent evidence from the World Health Organization and the European Centre for Disease Prevention and Control suggests that a large proportion of clade 3C.2a viruses are antigenically distinct from the egg-passaged version of the vaccine, suggesting some degree of antigenic mismatch in addition to genetic differences between circulating viruses and the 2015-16 H3N2 vaccine component.[14,15]

Implications for vaccine protection and antiviral recommendations:

Vaccine effectiveness (VE) estimates specific for the 2015-16 vaccine will not be available until at least mid-season (likely not before February 2016).

However, in a recent meta-analysis of 36 studies from the past decade that used the test-negative design to measure VE against virologically-confirmed influenza, the pooled VE for the A(H3N2) component was on average just 38% (95% confidence interval=31-44%).[16] Similar findings of recurrently low VE for the H3N2 component of influenza vaccine has also been reported by

Canada's Sentinel Practitioner Surveillance Network (SPSN) over the past decade, including negligible protection last season.[17] In combination with early-season indicators of genetic and antigenic differences between the vaccine and circulating viruses, similar to last season, these findings again raise concern about VE for the A(H3N2) component for the coming 2015-16 season.

The same meta-analysis identified pooled VE of 65% (95% confidence interval=60-68%) for influenza A(H1N1)pdm09 subtype viruses and 63% (95% confidence interval=56-69%) for influenza B;[16] however, these latter two kinds of viruses are far less common causes of institutional influenza outbreaks than the A(H3N2) subtype.

Historically, antiviral chemoprophylaxis has been recommended for unvaccinated but not vaccinated workers for the purpose of facility influenza outbreak control. These recommendations initially date back to a period when VE was reported to typically range 70-90% in healthy young adults,[19] but require review and update in the context of evolving understanding of the lower effectiveness and greater variability in vaccine performance by subtype, identified within the past decade. A large proportion (more than half *on average*) of vaccinated individuals are anticipated to remain at equivalent risk of influenza A(H3N2) infection as unvaccinated people. Conversely, the incremental value of additional healthcare worker antiviral chemoprophylaxis, over and above other standard influenza outbreak control measures requires review and assessment.

Pending that re-analysis, measures for facility influenza outbreak control that are considered the ongoing standard of care include: seasonal influenza vaccination of staff and residents (preferably pre-season); antiviral prophylaxis of all non-ill residents; early antiviral treatment of symptomatic individuals (workers or residents both vaccinated and unvaccinated); reinforced infection control measures including respiratory etiquette and use of personal protective equipment; and exclusion of ill staff or visitors and new admission deferral. Outbreak control measures also include antiviral chemoprophylaxis for unvaccinated staff; this may be extended to vaccinated staff as an option or at the discretion of the local health authority/Medical Officer of Health during outbreaks, notably those due to H3N2 viruses that may otherwise be poorly controlled by standard measures.

Antiviral resistance:

Oseltamivir and zanamivir resistance remains very low. Data from the US Centers for Disease Control and Prevention (CDC) surveillance for influenza virus resistance during the 2014-2015 season indicate that almost all strains of influenza A and B were susceptible to oseltamivir (98.4 %,100%, and 100% for subtypes A(H1N1)pdm09, A(H3N2), and type B) and zanamivir (100% for all A subtypes and type B).[19]

Intravenous Zanamivir and Peramivir:

Intravenous zanamivir is not yet licensed in Canada, but can be obtained through the Special Access Program at Health Canada. It should only be used in place of oral oseltamivir when there is suspect or proven oseltamivir resistance, OR in rare cases where effective absorption of oseltamivir cannot be anticipated when administered as a capsule or suspension by nasogastric or other enteric tube.

Peramivir is an oseltamivir-like intravenous neuraminidase inhibitor indicated for persons who cannot take oral oseltamivir by mouth or by nasogastric or other enteric tube. Influenza strains resistant to oseltamivir are also resistant to peramivir. It is not yet licensed in Canada.

Important points:

1. **In otherwise healthy individuals**, optimal benefits of oseltamivir or zanamivir occur when the drug is administered within 12 to 24 hours after the onset of symptoms of influenza. The earlier the better. After 48 hours, administration of these drugs confers little benefit.[20]
2. Data suggest that **in severely ill persons requiring hospitalization for influenza**, mortality is reduced with oral oseltamivir if administered even as late as 96 hours after the onset of symptoms, but again, the earlier the better.[21]
3. Oseltamivir for the purpose of influenza outbreak control should be initiated at the discretion of the local health authority/Medical Officer of Health, generally when 2 cases of influenza-like illness (ILI) (at least one confirmed as influenza) occur within 72 hours and continued for 14 days and/or until 7 days have elapsed since the last case was identified.[22]

4. The influenza drug amantadine should not be used for treatment or prophylaxis because of acquired resistance in all H1 and H3 influenza strains and inherent resistance in influenza B.
5. Pending updated evidence review and analysis, the extension of antiviral chemoprophylaxis recommendations to vaccinated as well as unvaccinated health care workers may be considered in long term facilities and acute care settings for the control of influenza outbreaks where these are otherwise poorly controlled by standard measures and/or in the context of suboptimal VE, notably for the A(H3N2) subtype.

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