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The epidemiology and spread of drug resistant human influenza viruses

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Significant changes in the circulation of antiviral-resistant influenza viruses have occurred over the last decade. The emergence and continued circulation of adamantane-resistant A(H3N2) and A(H1N1)pdm09 viruses mean that the adamantanes are no longer recommended for use. Resistance to the newer class of drugs, the neuraminidase inhibitors, is typically associated with poorer viral replication and transmission. But 'permissive' mutations, that compensated for impairment of viral function in A(H1N1) viruses during 2007/2008, enabled them to acquire the H275Y NA resistance mutation without fitness loss, resulting in their rapid global spread. Permissive mutations now appear to be present in A(H1N1)pdm09 viruses thereby increasing the risk that oseltamivir-resistant A(H1N1)pdm09 viruses may also spread globally, a concerning scenario given that oseltamivir is the most widely used influenza antiviral.

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Introduction

Influenza antivirals

While vaccination is the most traditional and widely utilised means of controlling influenza, antivirals that target specific proteins of the influenza virus are also important for treating or preventing influenza infections. Influenza antivirals play a particularly important role in the treatment of hospitalised or severely ill influenza patients and during the early stages of a pandemic when a suitably matched vaccine is unavailable [1]. Two classes of drugs with anti-influenza activity have been available in many countries over the past decade — the adamantanes, namely amantadine and rimantadine; and the neuraminidase inhibitors (NAIs), namely oseltamivir and zanamivir.

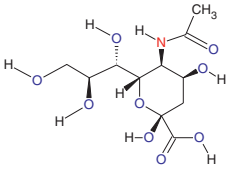
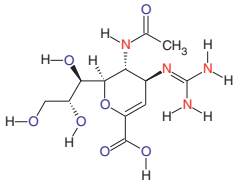
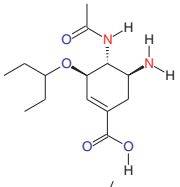
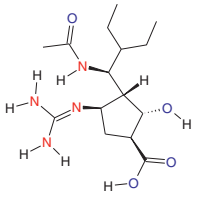
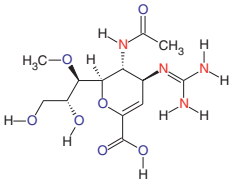
The adamantanes, amantadine and rimantadine, have been approved for clinical use since the 1960s and 1980s respectively, and act by blocking the M2 ion channel of influenza A viruses, a critical component required for viral replication. The adamantanes are not effective against influenza B viruses due to the difference in ion channel structure. Early studies that analysed patient samples post-adamantane treatment showed the propensity for both amantadine and rimantadine to rapidly select for resistant strains which had the capacity to spread readily within closed settings [2–5]. Importantly, resistance against one of the drugs (e.g. amantadine) resulted in complete cross resistance to the other (e.g. rimantadine). These early findings demonstrated the potential for adamantane-resistant viruses to spread into the community in the future.

The NAIs, which were developed in the 1990s, are sialic acid analogues which act by blocking the neuraminidase (NA), an enzymatic protein on the surface of the virus that is critical for release of newly formed virions from the host cell. In addition to orally administered oseltamivir and inhaled zanamivir, two new NAIs, peramivir and laninamivir, have been approved in Japan (and in the case of peramivir also South Korea) and are undergoing late-phase clinical trial in the USA and elsewhere. Peramivir is delivered intravenously and therefore is well suited for the treatment of critically ill patients [6], whereas laninamivir is a long acting inhaled drug, delivered as a single dose that remains active for five to seven days [7]. Although all four NAIs are based on the structure of sialic acid, there are some important differences (Figure 1), such that there is little cross resistance between oseltamivir and zanamivir, that is, resistance against oseltamivir generally does not alter zanamivir sensitivity. However, some cross resistance is observed between zanamivir and laninamivir, and between oseltamivir and peramivir depending on the location of the amino acid mutation in the NA active site.

Resistance and viral fitness — the ultimate combination

Due to the high mutation rate of influenza viruses during replication, there are ever-present opportunities for novel variant viruses to arise. On occasions these variant viruses contain mutations in the antiviral target proteins (i.e. the M2 ion channel or the NA) that can reduce drug binding and result in viruses that are considered to be resistant. However, the future success of those resistant viruses is largely dependent on their 'fitness' — their ability to replicate efficiently and transmit readily between hosts. Whilst the *relative* fitness of a resistant strain may be

Figure 1

	Structure	Structural features			
		Carboxylate group	Glycerol group	Guanidine group	Pentyl (hydrophobic) side group
Sialic Acid		✓	✓		
Zanamivir		✓	✓	✓	
Oseltamivir		✓			✓
Peramivir		✓		✓	✓
Laninamivir		✓	✓*	✓	

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Structural comparison of sialic acid and four neuraminidase inhibitors. The neuraminidase inhibitors (NAIs) are sialic acid analogues that have additional features which enable enhanced binding to the enzymatic site. The presence or absence of key structural features of the NAIs provides insight into how they bind to the enzymatic site and the effect that amino acid substitutions can have on drug binding. Oseltamivir and peramivir both share the hydrophobic pentyl ether group which, in the event of a H275Y NA mutation, means that both drugs demonstrate reduced binding to the enzymatic site of N1 neuraminidases. *Zanamivir and laninamivir share very similar structures, except that the glycerol side chain is modified by the addition of an alkyl group in laninamivir.

enhanced in patients undergoing antiviral treatment (due to drug inhibiting the competing sensitive viruses), if the *inherent* fitness of the virus (in the absence of drug pressure) is not high, it is unlikely to efficiently transmit and circulate widely amongst the community. While there are many examples of NAI-resistant viruses that have severely compromised viral fitness (e.g. A(H3N2) viruses with an R292K NA mutation) [8,9], it is those that replicate and transmit to equivalent or enhanced levels compared to wild type viruses that are the greatest public health concern. Over the past decade there have been numerous examples of adamantane-resistant or oseltamivir-resistant viruses emerging within the community. While some of these resistant viruses have occurred on