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Emerging novel and antimicrobial-resistant respiratory tract infections: new drug development and therapeutic options

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Lancet Infect Dis 2014; **14: 1136–49**

Published **Online** September 2, 2014 http://dx.doi.org/10.1016/S1473-3099(14)70828-X

See **Comment** *Lancet Infect Dis* 2014; **14:** 910–11

This is the fifth in a **Series** of five papers on emerging respiratory tract infections

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The emergence and spread of antimicrobial-resistant bacterial, viral, and fungal pathogens for which diminishing treatment options are available is of major global concern. New viral respiratory tract infections with epidemic potential, such as severe acute respiratory syndrome, swine-origin influenza A H1N1, and Middle East respiratory syndrome coronavirus infection, require development of new antiviral agents. The substantial rise in the global numbers of patients with respiratory tract infections caused by pan-antibiotic-resistant Gram-positive and Gram-negative bacteria, multidrug-resistant *Mycobacterium tuberculosis*, and multiazole-resistant fungi has focused attention on investments into development of new drugs and treatment regimens. Successful treatment outcomes for patients with respiratory tract infections across all health-care settings will necessitate rapid, precise diagnosis and more effective and pathogen-specific therapies. This Series paper describes the development and use of new antimicrobial agents and immune-based and host-directed therapies for a range of conventional and emerging viral, bacterial, and fungal causes of respiratory tract infections.

Introduction

The emergence of difficult-to-treat known and novel bacterial, viral, and fungal respiratory tract pathogens with epidemic potential is of major global concern. Treatment options are limited by increasing antimicrobial-drug resistance. However, new viral infections causing severe respiratory tract disease with pandemic potential have focused global attention.[1] A substantial rise in the number of patients with multidrug-resistant pulmonary tuberculosis[2] and pan-drug-resistant bacteria[3] has been noted. Increasing use of immunosuppressive agents, broad-spectrum antibiotics, and anticancer agents, coupled with resistance to azoles, has led to an increase in the number of invasive pulmonary fungal infections[4] with resultant high morbidity and mortality. Successful treatment outcomes for patients with respiratory tract infections across all health-care settings require appropriate, effective, and pathogen-specific drug or alternative treatments. We describe a range of conventional and emerging viral, bacterial, and fungal causes of respiratory tract infections for which new antimicrobial drugs and immune-based and host-directed therapies are being developed and studied.

Key messages

- Respiratory tract infections are among the top two causes of morbidity and mortality worldwide. Antimicrobial-resistant species of bacteria, viruses, and fungi continue to emerge globally.
- A substantial rise in the numbers of cases of multidrug-resistant bacteria, azole-resistant fungi, and oseltamivir-resistant influenza A H1N1 causing respiratory tract infections has been identified, showing the potential limitations of current antibiotic, antiviral, and antifungal treatments for severe respiratory tract infections.
- Epidemic waves of avian influenza A H7N9 virus, sporadic cases of avian influenza A H10N8, and the ongoing outbreak of Middle East respiratory syndrome coronavirus infection show an urgent need for the development of more effective antivirals.
- Research is focused on repurposing available antiviral drugs for generic or specific use, or combination use with other adjunct interventions such as immunomodulators and host-directed therapies.
- Only one class of effective antiviral agents are approved for prevention and treatment of influenza in most countries: neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, and laninamivir).
- Antibiotic treatment options are limited for pan-antibiotic resistant Gram-negative bacteria, and new antibacterial antibiotic pipeline remains thin.
- Increased investments into development of new antibacterial drugs and other antibacterial innovations and for more prudent use of existing antibiotics are required worldwide.
- Development of new therapeutic options needs to be coupled to international regulations on the use and prescription of antimicrobial drugs.

Viral respiratory tract infections

The outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV),[5] re-emergence of avian influenza A H5N1,[6] global circulation of oseltamivir-resistant seasonal influenza A H1N1,[7] and subsequent emergence of the pandemic influenza A H1N1 strain pdm09 virus (which continues to circulate),[8] have shown the potential limitations of current antiviral treatments for severe respiratory viral infections. Epidemic waves of avian influenza A H7N9,[9] sporadic cases of avian influenza A H10N8,[10] the ongoing outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection, and the burden of common respiratory viruses[11]—such as seasonal influenza, respiratory syncytial virus, rhinoviruses, and adenoviruses—show that the development of more effective therapies to reduce morbidity and mortality is urgently needed. Research is focused on the repurposing of available antiviral drugs for generic or specific use and for

	Spectrum	Main mechanism of action	Antiviral resistance in clinical influenza isolates	Route of delivery	Pharmacokinetic features	Main adverse effects
Amantadine	Influenza A	Inhibition of M2 ion channel function, preventing virion uncoating	Widespread*	Oral	High oral bioavailability; long plasma elimination half-life (8–12 h); renal excretion of unchanged drug; dose adjustment required in renal dysfunction	CNS effects (including confusion, seizure, and psychosis), gastrointestinal effects, hypotension
Rimantadine	Influenza A	Inhibition of M2 ion channel function, preventing virion uncoating	Widespread*	Oral	High oral bioavailability; prolonged plasma elimination half-life (≥24 h); hepatic metabolism and renal excretion; dose adjustment required in severe hepatic and renal dysfunction	Gastrointestinal effects, CNS effects (lower risk than amantadine)
Oseltamivir	Influenza A and B	Inhibition of enzymatic action of viral neuraminidase†	Uncommon (1–2% in community isolates)‡	Oral	Rapid absorption of ethyl ester prodrug (phosphate) with conversion by gastrointestinal tract, hepatic, and blood esterases to the active carboxylate; peak concentrations at 3–4 h; renal excretion of both; carboxylate plasma elimination half-life of 8–10 h; dose adjustment required in renal dysfunction and young children	Gastrointestinal effects, insomnia, CNS effects (rare); anaphylaxis, severe skin reactions (rare)
Zanamivir	Influenza A and B	Inhibition of enzymatic action of viral neuraminidase*	Rare (<0·001% of community isolates)	Inhaled, nebulised, intravenous	Commercial inhaler delivers roughly 15% to lower respiratory tract; sputum concentrations detectable to 24 h; systemic bioavailability less than 20%; intravenous zanamivir excreted renally with plasma elimination half-life of roughly 2 h; dose adjustment required in renal insufficiency	Cough, bronchospasm, allergic reactions; lactose-containing commercial formulation should not be used in patients undergoing mechanical ventilation
Peramivir§	Influenza A and B	Inhibition of enzymatic action of viral neuraminidase*	Uncommon	Intravenous	Median peak and trough plasma concentrations of around 51 500 μg/mL and 46 μg/mL after 600 mg dose; predominantly renal excretion; dose adjustment required in renal insufficiency	Gastrointestinal and possible CNS effects; decreased polymorphonuclear counts
Laninamivir¶	Influenza A and B	Inhibition of enzymatic action of viral neuraminidase*	Rare	Inhaled	Octanoate prodrug converted to laninamivir in airway, prolonged detection in epithelial lining fluid; systemic bioavailability roughly 15%; plasma elimination half-life of around 3 days	Gastrointestinal effects, dizziness
Favipiravir/T-705‖	Influenza A, B, and C and many other RNA viruses	Undergoes intracellular ribosylation and phosphorylation to active triphosphate form and selectively inhibits RNA-dependent RNA polymerase of influenza virus; also induces lethal mutagenesis	Not reported	Oral	Good oral bioavailability; parent metabolised to inactive moiety by host aldehyde oxidase and also inhibitor of aldehyde oxidase (favipiravir's metabolic enzyme); loading dose necessary; more than 65% excreted by kidneys as metabolite by 48 h	Dose-related hyperuricaemia; restricted use in pregnancy
DAS181	Influenza A and B and parainfluenza viruses	Sialidase that destroys receptors for viral haemagglutinin; novel fusion construct that includes the catalytic domain from *Actinomyces viscosus* sialidase linked with an epithelium-anchoring domain of human amphiregulin; this sialidase removes both α-2,6-linked and α-2,3-linked sialic acids from cellular receptors	Not reported	Inhaled	In ex-vivo human airway epithelium and human bronchial tissue, the inhibitory effect of DAS181 treatment lasts for 2 days or more; tracheobronchial delivery and degree of systemic absorption depend on particle size	Increased alkaline phosphatase because of reduced clearance; no associated increases in transaminases
Nitazoxanide	Influenza A and B and other RNA viruses	Inhibition of haemagglutinin maturation; immunomodulation and perhaps other antiviral actions.	Not reported	Oral	Plasma esterases metabolise it into active desacetyl derivative tizoxanide, which undergoes glucuronidation and urinary elimination with an elimination half-life of roughly 7 h; tizoxanide is highly bound (>99%) to plasma proteins; need for dose adjustments uncertain	Gastrointestinal effects, respiratory distress

*Resistance in seasonal influenza A H3N2 and 2009 pandemic influenza A H1N1; avian influenza A H7N9, A H10N8, and A H9N2; and some influenza A H5N1 viruses. †Neuraminidase inhibitors prevent destruction of sialic-acid-bearing receptors recognised by influenza A and B virus haemagglutinins. This action blocks virus from being released from infected cells and spreading through respiratory secretions to initiate new cycles of replication. Neuraminidase inhibitors might also inhibit virus binding to cells. ‡Except seasonal influenza A H1N1 during 2007–09. §Approved in China, Japan, and South Korea. ¶Approved in Japan. ‖Approved in Japan for treatment of novel or re-emerging influenza virus infections (restricted to cases in which other anti-influenza drugs are ineffective or not sufficiently effective).

Table 1: **Influenza antivirals approved or in advanced clinical development**