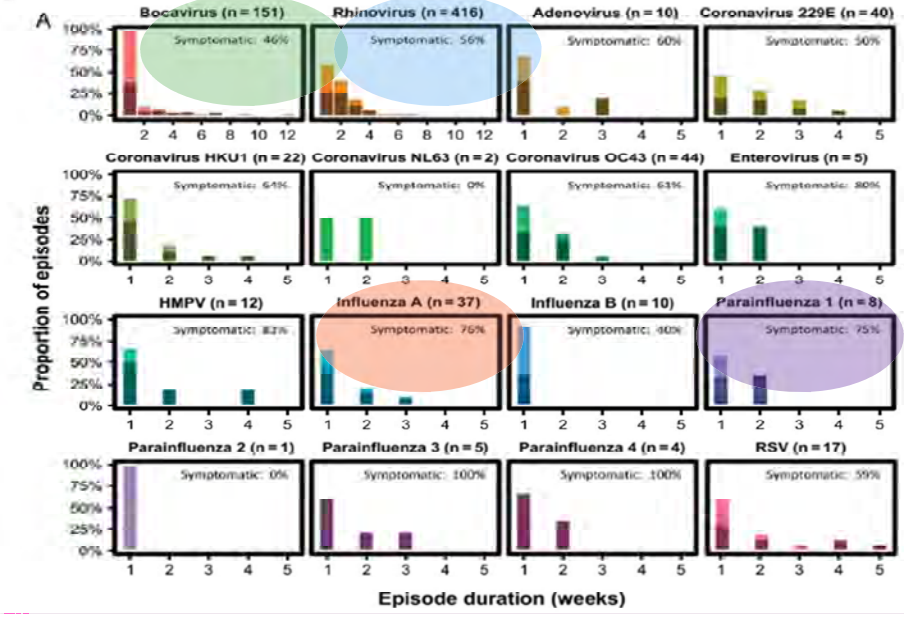

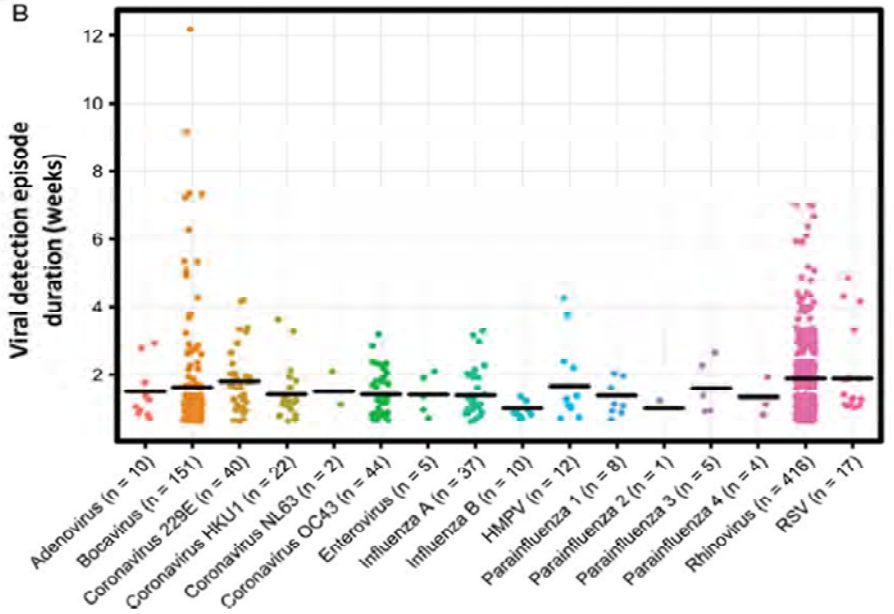

Human rhinoviruses: The cold wars resume

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Abstract

Background: Human rhinoviruses (HRVs) are the most common cause of viral illness worldwide but today, less than half the strains have been sequenced and only a handful examined structurally. This viral super-group, known for decades, has still to face the full force of a molecular biology onslaught. However, newly identified viruses (NIVs) including human metapneumovirus and bocavirus and emergent viruses including SARS-CoV have already been exhaustively scrutinized. The clinical impact of most respiratory NIVs is attributable to one or two major strains but there are 100+ distinct HRVs and, because we have never sought them independently, we must arbitrarily divide the literature's clinical impact findings among them. Early findings from infection studies and use of inefficient detection methods have shaped the way we think of 'common cold' viruses today.

Objectives: To review past HRV-related studies in order to put recent HRV discoveries into context.

Results: HRV infections result in undue antibiotic prescriptions, sizable healthcare-related expenditure and exacerbation of expiratory wheezing associated with hospital admission.

Conclusion: The finding of many divergent and previously unrecognized HRV strains has drawn attention and resources back to the most widespread and frequent infectious agent of humans; providing us the chance to seize the advantage in a decades-long cold war.

Mackay, et al. J Clin Virol 2008.

Baseline incidence of respiratory viruses in asymptomatic patients

Alicia Mitchell, Matthew Peters, Lucy Morgan, Brian Oliver

Methods: Asymptomatic patients undergoing bronchoscopy. A panel of respiratory virus (RV, RSV, Flu A B, PIV1, 2, 3 & HMP) was assayed using a sensitive RT-PCR.

Results: 50 bronchoscopies. 46% had a detectable virus. 21% had strongly positive detection. RV was the most commonly detected virus. 1 patient had 2 viruses (RV & Flu B).

Conclusion: This analysis suggests asymptomatic carriage of viruses may be more common that recognised & that resp virus likely contribute to the microbiome of the lung. Appropriate assay limits need to be established for clinically relevant results.

Eur Resp J 2016.

Limited Asymptomatic Carriage of *Pneumocystis jiroveci* in Human Immunodeficiency Virus–Infected Patients

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Forty-seven bronchoalveolar lavage fluid samples from 16 human immunodeficiency virus (HIV)–infected patients were used to test the latency model of *Pneumocystis* infection in the human host. Identification of DNA sequence polymorphisms at 4 independent loci were used to genotype *Pneumocystis jiroveci* from the 35 samples that contained detectable *P. jiroveci* DNA. Eighteen of those 35 samples came from patients who did not have *Pneumocystis* pneumonia (PCP) and had confirmed alternative diagnoses. Seven patients had asymptomatic carriage of *P. jiroveci* over periods of ≤9.5 months after an episode of PCP, and in all 7 cases, a change in genotype from that in the original episode of PCP was observed. The absence of *P. jiroveci* DNA in one-fourth of the 47 samples and the observed changes in genotype during asymptomatic carriage do not support the latency model of infection. Asymptomatic carriage in HIV-infected patients may play a role in transmission of *P. jiroveci* and may even supply a reservoir for future infections.

J Infect Dis 2003.

Use of the Polymerase Chain Reaction in the Diagnosis of Herpes Simplex Encephalitis: A Decision Analysis Model*

Pablo Tebas, MD, Robert F. Nease, PhD, Gregory A. Storch, MD

	Number of Subjects	Herpes Encephalitis Present (n = 160)		Herpes Encephalitis Not Present (n = 416)	
		PCR+	PCR−	PCR+	PCR−
Lakeman et al (20)	101	53	1	3	44
Aurelius et al (5)	130	41	2	0	87
Rozenberg et al (8)	65	27	1	0	37
Kessler et al (16)	123	16	0	0	107
Klapper et al (6)	22	9	1	0	12
Puchammer-Stockl et al (7)	20	4	1	0	15
Troendle-Atkins et al (11)	115	3	1	0	111
Total	576	153	7	3	413

Gold standard: brain biopsy or intrathecal Ab production

Ann Int Med 1998.

Summary of 4 patients w/ false positive CSF HSV PCR

Patient, age (years)	Clinical findings	Magnetic resonance imaging	PCR: Laboratory 1: Original	PCR: Laboratory 1: Repeat	PCR: Laboratory 2*	Final diagnosis
1, 35	Upper respiratory syndrome followed by extreme fatigue, 2 weeks later, blurred vision, headache, ophthalmoplegia and obstructive hydrocephalus; no response to acyclovir treatment	Enhancement in left basal ganglia, right thalamus, right pons, and midbrain	Positive ×3; detected by ethidium stain only	No sample available†	No sample available	Acute disseminated encephalomyelitis of unknown etiology
2, 35	AIDS patient with dermatomal herpes zoster followed in a few weeks by temporal lobe encephalitis that responded to acyclovir; 2 months later presented with VZV retinal necrosis	Massive right temporal lobe edema and inflammation	Positive; confirmed by Southern blot	Negative	Negative for HSV; positive for VZV	VZV encephalitis
3, 75	Cerebrovascular accident; history of atherosclerosis, myocardial infarction, hypertension, and diabetes; not treated with acyclovir; 6 months later admitted with femoral thrombosis	Left temporal mass with hemorrhage	Positive; confirmed by Southern blot	Positive	Negative	Cerebrovascular accident
4, 3	Severe developmental delay with possible seizure disorder; admitted with fever and neurologic deterioration	Increased ventricle size, diffuse demyelinating process and cortical atrophy	Positive; detected by ethidium stain only	Negative	Negative	Progressive metabolic or neurodegenerative disease

Landry ML. Yale U School of Medicine. J Infect Dis 1995.

Test performance for diagnosis

Low sensitivity, in some IDs

Bacteria

Test	Sensitivity	Specificity	Substance Detected
Toxigenic culture	High	Low[a]	*Clostridium difficile* vegetative cells or spores
Nucleic acid amplification tests	High	Low/moderate	*C. difficile* nucleic acid (toxin genes)
Glutamate dehydrogenase	High	Low[a]	*C. difficile* common antigen
Cell culture cytotoxicity neutralization assay	High	High	Free toxins
Toxin A and B enzyme immunoassays	Low	Moderate	Free toxins

Organism	Sensitivity	Specificity	Comments
Viruses			
Adenovirus	Unknown	Unknown	
Arboviruses WNV	Unknown (not standardized) 60%	Unknown	CSF serology is more sensitive
BK virus	Unknown	Unknown	
Enterovirus	>95%	>95%	
Herpesviruses CMV	82–100% in immunocompromised patients, ≤60% in congenital CMV infection	86–100%	Quantitation available to monitor response to therapy and predict disease severity
EBV	98.5% as tumor marker in HIV patients with CNS lymphoma	100%	Predictive value in normal hosts is unclear; quantitation available for monitoring response to therapy and possibly assessing risk of CNS disease in HIV patients
HHV-6	>95%		Poor positive predictive value for disease (30% positivity in normal hosts)
HSV-1 and -2	>95%	>95%	Quantitation available (see text for multiple uses)
VZV	80–95% in immunocompromised patients	>95%	
HIV	HIV RNA is present at all stages	>95%	Quantitation available, correlates with likelihood of neurologic disease, and is useful for monitoring response to antiretroviral therapy
HTLV-1 and -2	90% for HAM/TSP	90%	Quantitation available and may predict risk of neurologic disease
JC virus	30–75% for PML	98–100%	Quantitation available for assessing response to therapy and correlates with prognosis
Measles virus	Unknown	Unknown	Quantitation available to monitor load in SSPE patients in response to therapy
Rabies virus	100%	100%	
Nonviral entities in differential diagnosis			
Mycoplasma	Unknown		Sensitivity is difficult to assess in setting of clinical disease, since both active infection and autoimmune mechanisms of disease exist
M. tuberculosis	Variable (33–90%)	88–100%	
B. burgdorferi (Lyme disease)	17% for neuroborreliosis		Serologic diagnosis more sensitive
Toxoplasma	Variable (50–75%) in HIV patients	Variable	

DeBiasi & Tyler, U of Colorado Health Sciences Ctr.
Clin Microbiol Rev 2004.

Diagnosis in fungal infection

Culture: gold standard

Molecular microbiology

- Alternative

Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group

Ben De Pauw,* Thomas J. Walsh,* J. Peter Donnelly,* David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Muñoz, Frank C. Odds, John R. Perfect, Angela Restrepo, Markus Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, and John E. Bennett[a]

Analysis and specimen	Molds[a]	Yeasts[a]
Microscopic analysis: sterile material	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells—for example, *Cryptococcus* species indicated by encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[c]
Culture		
Sterile material	Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process
Blood	Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process	Blood culture that yields yeast (e.g., *Cryptococcus* or *Candida* species) or yeast-like fungi (e.g., *Trichosporon* species)
Serological analysis: CSF	Not applicable	Cryptococcal antigen in CSF indicates disseminated cryptococcosis

Host factors[a]

Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease

Receipt of an allogeneic stem cell transplant

Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks

Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days

Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

Mycological criteria

Direct test (cytology, direct microscopy, or culture)

Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:

Presence of fungal elements indicating a mold

Recovery by culture of a mold (e.g., *Aspergillus, Fusarium,* Zygomycetes, or *Scedosporium* species)

Indirect tests (detection of antigen or cell-wall constituents)[e]

Aspergillosis

Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF

Invasive fungal disease other than cryptococcosis and zygomycoses

β-D-glucan detected in serum

Meningeal enhancement on MRI or CT

Disseminated candidiasis[d]

At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:

Small, target-like abscesses (bull's-eye lesions) in liver or spleen

Progressive retinal exudates on ophthalmologic examination

Mycological criteria

Direct test (cytology, direct microscopy, or culture)

Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:

Presence of fungal elements indicating a mold

Recovery by culture of a mold (e.g., *Aspergillus, Fusarium,* Zygomycetes, or *Scedosporium* species)

Indirect tests (detection of antigen or cell-wall constituents)[e]

Aspergillosis

Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF

Invasive fungal disease other than cryptococcosis and zygomycoses

β-D-glucan detected in serum

Diagnosis and criteria

Proven endemic mycosis

In a host with an illness consistent with an endemic mycosis, 1 of the following:

Recovery in culture from a specimen obtained from the affected site or from blood

Histopathologic or direct microscopic demonstration of appropriate morphologic forms with a truly distinctive appearance characteristic of dimorphic fungi, such as *Coccidioides* species spherules, *Blastomyces dermatitidis* thick-walled broad-based budding yeasts, *Paracoccidioides brasiliensis* multiple budding yeast cells, and, in the case of histoplasmosis, the presence of characteristic intracellular yeast forms in a phagocyte in a peripheral blood smear or in tissue macrophages

For coccidioidomycosis, demonstration of coccidioidal antibody in CSF, or a 2-dilution rise measured in 2 consecutive blood samples tested concurrently in the setting of an ongoing infectious disease process

For paracoccidioidomycosis, demonstration in 2 consecutive serum samples of a precipitin band to paracoccidioidin concurrently in the setting of an ongoing infectious disease process

Probable endemic mycosis

Presence of a host factor, including but not limited to those specified in table 2, plus a clinical picture consistent with endemic mycosis and mycological evidence, such as a positive *Histoplasma* antigen test result from urine, blood, or CSF

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King Chulalongkorn Memorial Hospital, Thai Red Cross Society

Bacteria, fungus, virus, protozoa & other organisms

- **Conventional diagnostics: clinical use**
  - Gold standard in general esp in **bacteria & fungus**
  - Widely available
  - Economical
  - Practical
  - Simple (nonlabor intensive)

Department of Medicine
Faculty of Medicine, Chulalongkorn University
King Chulalongkorn Memorial Hospital, Thai Red Cross Society

Problems w/ sensitivity & specificity variation in

specimen, virus, types/gene target of molecular technology

Ginocchio CC, et al. Current best practices for respiratory virus testing. J Clin Microbiol. 2011.