



ERS | *monograph*

SARS, MERS and other
Viral Lung Infections

Edited by
David S. Hui,
Giovanni A. Rossi and
Sebastian L. Johnston

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Editor in Chief
Robert Bals

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Preface

Robert Bals

There is an ongoing debate whether viruses can be classified as life forms as they lack the characteristics (*e.g.* cell body or autarkic replication) of eukaryotic or prokaryotic cells. The emergence of viruses in evolutionary terms is also unclear; it is likely they have advanced from bacterial plasmids or other parts of nucleic acids. Virology was founded when Dmitri Ivanovsky and Martinus Beijerinck discovered plant viruses at the end of the 19th century. Viruses comprise complex particles that infect bacterial, plant and animal cells. They are classified by their genome (where ss is single stranded and ds is double stranded, according to the Baltimore classification) into dsDNA viruses, ssDNA viruses, dsRNA viruses, (+)ssRNA viruses, (–)ssRNA viruses, ssRNA-RT viruses and dsDNA-RT viruses. The classification of the International Committee on Taxonomy of Viruses (ICTV) divides virus by their biological properties into orders, families and so on. The morphologies of viruses are very diverse and comprise viruses with or without lipid cover and multiple shapes.



As the biological complexity of viruses unfolds, the pulmonary physician continues to face viral infections in daily practice: 1) typical respiratory viruses, such as influenza, rhinovirus or RSV, which cause common infectious diseases; 2) new viruses, which often originate in animals, become a threat to mankind and cause outbreaks (SARS-CoV and MERS-CoV); 3) immunocompromised patients who are susceptible to a wide range of viral species (CMV and herpes simplex virus); and 4) respiratory viruses and newly identified viruses, which have been shown to impact on the development of non-communicable diseases, such as asthma, COPD and perhaps cancer. Viral infections therefore play an important role in respiratory medicine and are within the main focus of public health activities.

This *ERS Monograph* considers viral infections of the respiratory tract with a focus on newly emerged viruses. There are chapters on SARS-CoV, MERS-CoV and avian influenza, as well as more common viral pathogens, such as seasonal influenza and rhinovirus.

The chapters present comprehensive information about the biology, diagnosis and treatment of the disease, and are written by experts in the field of world renown.

The European Respiratory Society is a partner of the Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) (<http://www.prepare-europe.eu>), which is funded by the European Commission's 7th Framework Programme for Research and Technological Development (FP7) project. PREPARE aims to harmonise large-scale clinical research studies on infectious diseases, and is prepared to respond to severe infectious disease outbreak rapidly, in order to provide real-time evidence for clinical patient management and inform public health responses. PREPARE is a driving force in this area: it has already launched a range of interventional and observational inter-pandemic trials, and is working to reduce logistical, regulatory and administrative bottlenecks to speed the rapid implementation of clinical trials. With this initiative in mind, an *ERS Monograph* on viral diseases is very well timed.

The Guest Editors, David S. Hui, Giovanni A. Rossi and Sebastian L. Johnston have worked very successfully to integrate the selected topics into a comprehensive book that presents the current knowledge on viral infection. I would like to thank the Guest Editors and all the authors for their work on this excellent book. I am sure that this comprehensive review will be useful for the clinical practice of a broad range of respiratory physicians.

Disclosures: R. Bals has received grants from the German Research Ministerium and the Deutsche Forschungsgemeinschaft. He has also received personal fees from GSK, AstraZeneca, Boehringer Ingelheim and CSL Behring.



Guest Editors

David S. Hui

David S. Hui is the Stanley Ho Professor of Respiratory Medicine and Director of the Stanley Ho Centre for Emerging Infections Diseases at the Chinese University of Hong Kong (Shatin, Hong Kong).

He graduated from the University of New South Wales (Kensington, Australia) in 1985. He then trained in respiratory medicine and sleep medicine in Sydney, Australia. He was heavily involved in the clinical management of patients with SARS at the Prince of Wales Hospital (Shatin, Hong Kong) during the major outbreak in 2003. He served as a World Health Organization (WHO) advisor, reviewing the clinical management of avian influenza A(H5N1) during the early human outbreak in Vietnam in February 2004, and has since been a regular advisor to the WHO on the clinical management of SARIs. He has contributed to WHO treatment guidelines (including those for the influenza A(H5N1) virus in 2007, the influenza A(H1N1) pandemic in 2009, and MERS in 2013) and the WHO training workshop on the clinical management of influenza A(H7N9) and other SARIs in May 2014. He was a member of the urgent WHO missions investigating the outbreaks of MERS in Saudi Arabia and South Korea in 2013 and 2015, respectively.



David Hui's research interests include the clinical management of emerging SARIs, the safety of respiratory therapy in the post-SARS era, the efficacy of medical ward airflow in preventing nosocomial infections, sleep disordered breathing, and common airway diseases.

Giovanni A. Rossi

Giovanni A. Rossi is the former chief of the Pulmonary and Allergy units and of the Cystic Fibrosis Centre at the G. Gaslini Research Institute and University Hospital (Genoa, Italy) and the former adjunct Professor of Paediatric Pulmonology at the University of Genoa (Genoa). He is now Chief Emeritus at the G. Gaslini Research Institute.



Giovanni Rossi was Head of the Lung Cell Biology Assembly and a member of the Executive Committee of the European Respiratory Society, of which he has recently been appointed Foundation Fellow. He also served as an associate editor on the editorial boards of several other respiratory, allergy and paediatric journals and has published >290 manuscripts in peer reviewed journals.

His major areas of basic and clinical research have been the mechanisms involved in the pathogenesis of a variety of respiratory disorders, including the interstitial, obstructive and infectious diseases. In the latter, his work has focused mainly on the characterisation of the host-virus interaction at the lower respiratory tract level, with the aim of developing novel strategies for the prevention and treatment of these high-impact respiratory disorders for which specific therapies are often not yet available.

Sebastian L. Johnston



Sebastian L. Johnston is Professor of Respiratory Medicine and Allergy at the National Heart and Lung Institute, Imperial College London (London, UK). He is Director of the MRC and Asthma UK Centre in Allergic Mechanisms of Asthma (London), is the Asthma UK Clinical Professor and is a former European Research Council Advanced Grant holder. He is also a UK National Institute of Health Research Senior Investigator.

Sebastian Johnston edited *Thorax* from 2002 to 2010 and serves as an associate editor on the editorial boards of several other respiratory and allergy journals. He has published >380 scholarly manuscripts in peer reviewed journals and has 18 patents.

Notable discoveries that have emerged from his work include establishing the viral aetiology of the majority of asthma and COPD exacerbations, discovering novel mechanisms of susceptibility to virus infection in asthma and COPD, and developing novel treatment approaches for acute exacerbations of these diseases.

Sebastian Johnston is committed to capacity building for academia, industry and health services by training new basic and clinical investigators in asthma and COPD research. He also plays a significant role in public engagement and communication in the public domain.

Introduction

David S. Hui^{1,2}, Giovanni A. Rossi³ and Sebastian L. Johnston⁴

Viral respiratory tract infections are important and common causes of morbidity and mortality worldwide. Over the past two decades, several novel viral respiratory infections with epidemic potential that threaten global health security have emerged. Human cases of the highly pathogenic avian influenza A(H5N1) were initially detected in Hong Kong in 1997, before spreading to other parts of Asia, the Middle East, Europe and Africa, with a case fatality rate close to 60%. Influenza A(H1N1)pdm09 virus first emerged in 2009 as a novel swine-origin strain, which rapidly led to a pandemic and has remained a common circulating strain in many parts of the world. Human infections with the novel avian influenza A(H7N9) virus were first reported in mainland China in March 2013 and the infection has since spread to Hong Kong and Taiwan. Avian influenza A(H5N1) and A(H7N9) viruses have continued to circulate widely in some poultry populations and infect humans sporadically; sporadic human cases of avian A(H5N6), A(H10N8) and A(H6N1) have also emerged.

In March 2003, the World Health Organization (WHO) issued a global alert about an emerging SARS caused by a novel CoV, which rapidly spread from mainland China *via* Hong Kong to at least 29 countries/regions and finally ended in July 2003, with 8096 probable cases and 774 deaths. Since its first discovery in a patient who died of severe pneumonia in Saudi Arabia in 2012, MERS-CoV has spread to 26 countries. The mortality rates of MERS-CoV infection are high, especially in those with comorbid disease.

In addition to the threat of novel CoV and avian influenza viruses, the burden of the common respiratory viruses, such as seasonal influenza, RSV and human rhinoviruses (HRV), on healthcare utilisation remains high, and yet is also a largely unmet medical need. This highlights the urgent need for developing more effective therapies in order to reduce the morbidity and mortality associated with novel threats, as well as the regular offenders.

The Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) (<http://www.prepare-europe.eu/>) is an European Union funded network aiming to harmonise large-scale clinical research studies on infectious diseases, and provide real-time evidence for clinical management of patients and for informing public health responses. To advance our understanding of the clinical, epidemiological and scientific aspects of important respiratory viruses and facilitate planning of research studies on emerging

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infectious diseases, this *ERS Monograph* aims to provide an up-to-date and comprehensive overview of SARS, MERS and other viral respiratory infections, including seasonal influenza, avian influenza, RSV and HRV through six chapters written by authoritative experts from around the globe. We are most grateful to all the authors for their enormous contribution to this excellent book. We believe the selected topics will be of immense interest to all clinicians and scientists in the field.

Disclosures: S.L. Johnston reports receiving grants and personal fees from Centocor, Sanofi Pasteur, GSK, Chiesi, Boehringer Ingelheim and Novartis. He has also received personal fees from Grünenthal. He has received grants, personal fees and holds shares in Synairgen. In addition, S.L. Johnston has the following licensed patents. Blair ED, Killington RA, Rowlands DJ, Clarke NJ, Johnston SL. Transgenic animal models of HRV with human ICAM-1 sequences. UK patent application no. 02 167 29.4, 18 July 2002 and International patent application No. PCT/EP2003/007939, 17 July 2003; Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases. UK patent application no. GB 0405634.7, 12 March 2004; Wark PA, Johnston SL, Holgate ST, Davies DE. Interferon-beta for anti-virus therapy for respiratory diseases. International patent application no. PCT/GB05/50031, 12 March 2004; Wark PA, Johnston SL, Holgate ST, Davies DE. The use of interferon lambda for the treatment and prevention of virally-induced exacerbation in asthma and chronic pulmonary obstructive disease. UK patent application no. 0518425.4, 9 September 2005; Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases. US patent application - 11/517,763, patent no. 7569216, national phase of PCT/GB2005/050031, 04 August 2009; Wark PA, Johnston SL, Holgate ST, Davies DE. Interferon-beta for anti-virus therapy for respiratory diseases. European patent number 1734987, 5 May 2010; Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases (IFN β therapy) Hong Kong patent number 1097181, 31 August 2010; Wark PA, Johnston SL, Holgate ST, Davies DE. Anti-virus therapy for respiratory diseases (IFN β therapy). Japanese patent number 4807526, 26 August 2011; Wark PA, Johnston SL, Holgate ST, Davies DE. Interferon-beta for anti-Virus therapy for respiratory diseases. New Hong Kong - Divisional patent application no. 11100187.0, 10 January 2011. S.L. Johnston also has the following patent pending. Burdin N, Almond J, Lecouturier V, Girerd-Chambaz Y, Guy B, Bartlett N, Walton R, McLean G, Glanville N, Johnston SL. Induction of cross-reactive cellular response against rhinovirus antigens. European Patent Number 13305152, 4 April 2013.

List of abbreviations

ARDS	acute respiratory distress syndrome
ARI	acute respiratory infection
BOOP	bronchiolitis obliterans organising pneumonia
CMV	cytomegalovirus
COP	cryptogenic organising pneumonia
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
ICU	intensive care unit
IFN	interferon
Ig	immunoglobulin
IL	interleukin
ILI	influenza-like illness
MCP	monocyte chemoattractant protein
MERS	Middle East respiratory syndrome
RCT	randomised controlled trial
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
SARI	severe acute respiratory infection
SARS	severe acute respiratory syndrome
TLR	Toll-like receptors
TNF	tumour necrosis factor