

Evidence of human metapneumovirus in Australian children

Michael D Nissen,* David J Siebert,[†]
Ian M Mackay,[‡] Theo P Sloots,[§]
Stephen J Withers[¶]

* Director of Infectious Diseases, Royal Children's Hospital, Herston Road, Herston, QLD 4029 † Director of Virology, Queensland Health Pathology Service, Royal Brisbane Hospital Complex, QLD; ‡ PhD Research Scholar; § Head, Clinical Virology Research Unit, Sir Albert Sakzewski Viral Research Centre, Royal Children's Hospital, Herston, QLD; ¶ Director of Paediatrics, Logan Hospital, Logan, QLD. theniss@mailbox.uq.edu.au

TO THE EDITOR: We wish to report the identification of a novel virus causing lower respiratory tract disease in Australian children. The presence of this virus was recently described in Dutch children and tentatively called human metapneumovirus (hMPV).¹ Clinical symptoms of infection are reported to resemble those of human respiratory syncytial virus (hRSV) infection. We therefore investigated whether the virus was present in Australian children.

Three isolates were identified from a random selection of 200 nasopharyngeal aspirate (NPA) specimens collected throughout 2001 from children presenting to the Royal Children's Hospital, Brisbane, or the Logan Hospital, a public hospital to the south of Brisbane, with clinical respiratory tract disease. All NPA specimens were initially negative for hRSV, influenza A and B, parainfluenza 1, 2 and 3 and adenovirus by direct fluorescent antigen testing and subsequent viral culture. These negative NPA specimens were then screened by polymerase chain reaction (PCR) for hMPV, based on the known sequence of the virus.² Sequencing of the PCR product in all three positive samples was 100%

homologous with the known hMPV sequence. Viral growth was subsequently detected in culture from two of these samples, and confirmed as hMPV, using the method of van den Hoogen et al.¹ Co-existent infection with coronavirus, rhinovirus, *Bordetella pertussis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* was excluded by PCR screening of the three hMPV isolates using validated in-house methods based on established protocols. Clinical features of the infected children are summarised in the Box.

This is the first report of the presence of hMPV infection in Australian children and describes a new viral respiratory syndrome. It also adds to the clinical spectrum and understanding of respiratory viruses causing acute bronchiolitis in children. Only 25%–33% of NPA specimens collected from our population with suspected respiratory tract disease yield a positive result for a known viral or bacterial pathogen. Clinical features in this small cohort are difficult to separate retrospectively from hRSV.

Based on the findings of this limited preliminary study of children presenting to hospital with respiratory tract symptoms, we would predict that hMPV is also relatively common in the Australian community. We are currently undertaking further characterisation of the hMPV isolates, a more detailed study of the epidemiology of hMPV disease, as well as developing improved diagnostic assays to rapidly identify clinical cases and assess seroprevalence of immunity to hMPV.

1. van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nature Med* 2001; 7: 719–724.

2. Genbank. Human metapneumovirus. Accession numbers AF371330–AF371367. National Center for Biotechnology Information, National Institutes of Health, Bethesda, MD, USA. □

Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis

James C Hurley

General Medicine and Infectious Diseases Physician, 20 Drummond St North, Ballarat, VIC 3350. drjameshurley@bigpond.com

TO THE EDITOR: I write to offer a re-analysis of the data presented by Whitby and colleagues.¹ They reported a meta-analysis of crude estimates and relative risk of death derived from nine published studies for *Staphylococcus aureus* bacteraemia. They concluded that bacteraemia caused by methicillin-resistant *S. aureus* (MRSA) is associated with a “real increase in risk of death” compared with bacteraemia caused by methicillin-sensitive *S. aureus* (MSSA), with a relative risk of 2.12. However, they failed to explore fully the possible confounding effect of the patients' underlying diseases and treatment in their analysis.

With this in mind, I offer a re-analysis of their data using regression analysis. Mortality rates versus median length of stay in hospital before bacteraemia (LOS) are shown in the Box (next page) for the five studies for which these data were presented by Whitby et al (in Boxes 1 and 2). The four studies without LOS data were combined, using the median LOS from the other five studies in the figure and the regression model.

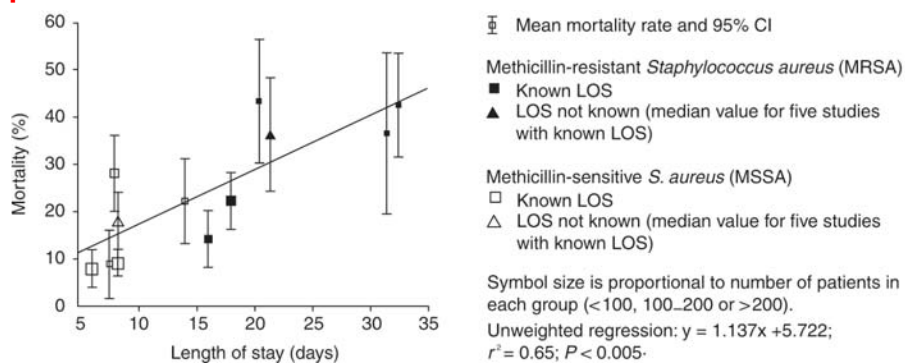
The regression analysis was performed with and without the weights provided by Whitby et al (Box 2), and also with and without the four studies for which LOS data were not available.

Regression analysis revealed a significant association between mortality rate and LOS ($P < 0.005$). However, the addition of

Clinical features of human metapneumovirus in three Australian children

	Case 1 (Girl, 12 months)	Case 2 (Boy, 5 years 11 months)	Case 3 (Boy, 20 months)
Date of nasopharyngeal aspirate collection	17/2/01	21/3/01	11/5/01
Presenting symptoms	Rhinorrhoea, cough, tachypnoea, wheeze, vomiting	Rhinorrhoea, cough, pharyngitis, conjunctivitis	Rhinorrhoea, cough, fever
Symptom duration before presentation (days)	4	3	4
Clinical signs	Respiratory distress with hypoxia, rhinorrhoea, pharyngitis, chest wheeze with crackles	Pharyngitis, chest wheeze	Rhinorrhoea, pharyngitis, chest wheeze, cervical lymphadenopathy
Chest X-ray	Not performed	Bilateral parahilar pneumonic infiltrates	Bilateral parahilar pneumonic infiltrates
Clinical diagnosis	Bronchiolitis	Viral lower respiratory tract infection	Viral lower respiratory tract infection
Outcome	Admitted for oxygen therapy and nasal suctioning for three days	Symptomatic treatment at home	Symptomatic treatment at home

Mortality rate versus hospital length of stay before bacteraemia (LOS) in patients with MRSA or MSSA bacteraemia



group status (MRSA or MSSA) failed to achieve significance in any iteration of the regression, while LOS remained a significant predictor of mortality risk.

This suggests that, with *S. aureus* bacteraemia, mortality rate increases with length of time in hospital before the bacteraemia. The likely explanation is that patients residing in hospital for longer periods are sicker. Moreover, they are more likely to have been exposed to antibiotics, leading to increased risk of acquiring an *S. aureus* strain that is methicillin-resistant. The mortality risk is no different for MRSA versus MSSA bacteraemia if LOS, a surrogate marker for severity of patient illness, is taken into account. The difference that Whitby et al observed between the groups of patients with MRSA and MSSA bacteraemia could be accounted for by the difference in LOS between these groups.

1. Whitby M, McLaws M-L, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis. *Med J Aust* 2001; 175: 264-267. □

Michael Whitby,* Mary-Louise McLaws,† Geoffrey Berry‡

* Director, Infection Management Services, Princess Alexandra Hospital, Ipswich Road, Brisbane, QLD 4102; † Director, NSW Hospital Infection, Epidemiology and Surveillance Unit, University of New South Wales, Sydney, NSW; ‡ Professor in Epidemiology and Biostatistics, University of Sydney, NSW. whitby@health.qld.gov.au

IN REPLY: We thank Hurley for his comments on our meta-analysis.¹ However, we strongly dispute that our analytical technique is flawed, and argue that we have been extremely cautious in drawing our conclusions. Hurley's contention is that hospital length of stay before bacteraemia (LOS) is a surrogate for severity of underlying disease and risk for colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA), and that these factors explain the higher mortality in patients with MRSA.

We agree that LOH may be a confounder. It may be an effect modifier, whereby patients in hospital for longer may be more ill, and therefore more susceptible to infection with and death from MRSA. Both are intuitive and biologically plausible conclusions. In fact, we referred to these possibilities in our Discussion, writing that "patients who ultimately become infected with MRSA are more seriously ill than those who become infected with MSSA [methicillin-sensitive *S. aureus*]" and "separating the effect of the bacteraemia *per se* from the effects of patients' underlying disease and treatment is a major problem when comparing outcomes". We also cautioned readers that available published data on mortality made it impossible for us to adjust for numerous potential confounders, including LOH, as the information given did not link these potential confounders with the outcome in individual patients.

Hurley has not, as he suggests, undertaken an analysis that would allow him to control correctly for the potential confounder, LOH. He, like us, used "group-as-a-unit" data, but, although the groups are homogeneous for MRSA or MSSA, they are heterogeneous for LOH. Adequate examination of and control for potential confounders requires either individual patient data or data from homogeneous groups. Hurley has attempted to use analysis normally reserved for individual data.⁴ His analysis was analogous to treating the data as though from an ecological study, a design in which control of confounding is difficult,⁵ and thus does not permit him to draw his conclusions.

Our analysis (not presented in our original article) of only those studies where the authors attributed mortality to bacteraemia⁶⁻⁸ found that the magnitude of effect remained (fixed-effect relative risk, 2.27; 95% CI, 1.75-2.96; $P < 0.001$; test for heterogeneity, $\chi^2 = 6.14$, $df = 4$, $P = 0.19$).

As MRSA bacteraemia is a rare event and published studies are small, the statistical ability to control for confounding and effect modification is limited. Until sufficient suitable data for individual patients are available for analysis, we have remained restrained in our assessment. Mindful that MRSA bacteraemia is associated with increased mortality, regardless of the cause, we hold with our original conclusion that "our findings justify ongoing surveillance and proactive management of MRSA in healthcare facilities".

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PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension

Ben D Ewald,* Brita Pekarsky†

* Lecturer in Epidemiology, Centre for Clinical Epidemiology, University of Newcastle, David Maddison Building, Watt St, Newcastle, NSW 2300; † Senior Lecturer in Health Economics, Department of General Practice, University of Adelaide, Adelaide, SA. bewald@cceb.newcastle.edu.au

TO THE EDITOR: The article by Nelson et al¹ estimates Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme (PBS/RPBS) savings if hypertensive patients on monotherapy were prescribed the agents recommended in guidelines; however, the analysis contains algebraic errors and insufficient sensitivity analyses. The question of excessive costs through the use of expensive agents for which there is no evidence of increased benefit for most patients is an important one, but the estimates of extent of overuse should be methodologically sound. The