



## The influenza conundrum

*It was the best of times, it was the worst of times...*

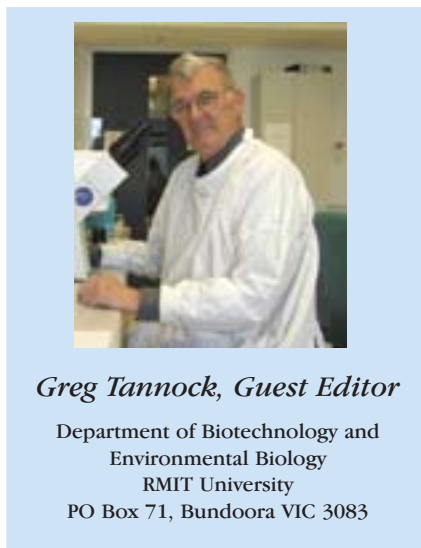
Charles Dickens: A tale of two cities

These lines are, in some ways, apposite to the current situation with pandemic influenza. We live in an age of great erudition with respect to the structure and replication of influenza viruses. We have much insight as to the immunology and pathogenicity of influenza viruses from studies in mice (albeit largely of viruses that are very different from contemporary epidemic strains). Knowledge of the crystalline structure of the two surface glycoproteins, the haemagglutinin and the neuraminidase, has facilitated considerable understanding of the mechanisms of antigenic variability and has allowed the development of neuraminidase inhibitors – the most effective antivirals ever developed for treatment of the disease.

In recognition that influenza is a truly international disease, there is now a highly developed network of reference laboratories which provide rapid intelligence as to changes in epidemic viruses. The recent emergence of avian influenza has led to coordinated national and international plans in anticipation of a catastrophic event, such as the 1918-19 pandemic.

However, global vaccine availability remains an unfulfilled dream and most plans for vaccine delivery are still decided on a purely national basis. Nevertheless, given the now truly international nature of vaccine manufacture, it seems reasonable to hope that future plans may have a larger element of collaboration between countries than exists today.

For inter-pandemic vaccines, availability is constrained by the need to manufacture new vaccines each year and the relatively high costs of antigen manufacture for inactivated vaccines that require, in the main, large numbers of embryonated eggs for virus growth. Alternative approaches, using suitable cell lines as substrates for virus growth, are being pursued with vigour by several manufacturers.



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Cell culture-derived vaccines have the potential to bring much greater flexibility to the manufacturing process. However, at present, they represent only a small fraction of the total world supply. In the event of the need for a widely available avian H5N1 vaccine, the situation could be further complicated by the need to use more than one dose due to the relatively poor immunogenicity of the H5 protective haemagglutinin antigen. Because of these constraints and the relatively small number of vaccine manufacturers, influenza vaccination seems likely to remain an option only for the developed world.

In Australia we are singularly well placed to combat pandemic and non-pandemic influenza. We have a well developed national pandemic plan with a high degree of federal and State government involvement and a very large number of associated agencies. Those behind the taskforce have, over the past 3 years, given much consideration to resource issues concerning hospital emergencies, border security and possible restrictions to movement within and without the country, much of which is covered in this issue. In particular, a national stockpile of approximately four million courses of the antineuraminidase drug oseltamivir has been set aside for emergency use in the early days of any new pandemic. As a developed and relatively wealthy country, we have good diagnostic infrastructure,

an experienced local vaccine manufacturer and considerable access to international manufacturers. As microbiologists, it is worth considering that much excellent research is being currently undertaken in Australia on the immunology of influenza but we have largely lost our former eminent position in basic influenza virology. Resource allocations in recent years towards research on HIV and the hepatitis viruses are largely responsible for this and the situation is by no means unique to Australia. However, there are reasons for believing that this issue is understood by government and that steps will be undertaken to redress the situation.

Why then is there any reason for pessimism? Well, despite heroic efforts, we cannot yet anticipate the triggering events that would introduce new pandemic viruses to the world or even inter-pandemic strains that can only be examined through the prism of retrospectivity! Furthermore, in today's world of rapid people movement, it seems reasonable to assume that a pandemic virus would have greatly increased opportunities to spread to susceptible populations than was the case in 1918-19. Although vaccine supplies will be greatly expanded in the years to come, it seems likely that coverage of only a small fraction of the world population will be met. The assumption is made that influenza vaccines will always be highly effective – something we cannot take for granted in key groups such as the elderly. Even the assumed role of modern antivirals in blunting the impact of a pandemic has never been put to the test.

However, as with HIV-AIDS and currently hepatitis viruses, the threat from an emerging pandemic has focussed the minds of research communities in many countries and it seems reasonable to hope that, among other things, improved vaccines – the most effective of all potential public health options – will eventually become available. As such, and if we are spared a pandemic for reasons that are not yet understood, then the second of Dickens' assertions may not prove to be correct!