Severe Acute Respiratory Syndrome (SARS)

Report of the working group meetings held at the Academy of Medical Sciences offices at 10 Carlton House Terrace, London on 9 June and 13 November 2003.

The Academy convened a meeting in London on 9 June to consider the recent SARS outbreak. Working group members were invited to take stock of current activity in the UK and worldwide and to identify ongoing concerns or issues for further work. The group was chaired by Professor Tony Minson, FMedSci, Professor of Virology in the University of Cambridge. A full list of members is given in appendix 1. A follow-up meeting was held on 13 November 2003.

Report of the Meeting held on 9 June 2003

International position/data collection

Infection rates are slowing and can be concluded to be under control, although there is still uncertainty about China because of the limited information available. The most affected countries initiated very large public health interventions that would not be sustainable in the longer term. In lesser-affected countries, there is a problem of "high noise to signal" ratio in data collection and comparisons are complicated by different national policies in declaring suspect cases. The predictive value of clinical diagnosis is likely to be high in those countries with high infection rates but less in countries such as the UK because of the higher "noise" level.

One continuing issue is the lack of consistency in case confirmation by laboratory testing (seroconversion, PCR) and it remains important to standardise quality control across all regional laboratories globally.

Crisis management

The WHO performed well and there was generally good international collaboration. There is an issue relating to problems of linkage between datasets (different professional groups): there was successful laboratory collaboration between virologists and (to a lesser extent) between epidemiologists but there are concerns about database integration between laboratory sampling and clinical case finding and between virology and epidemiology. The weakness in linkage is a problem for crisis management – the real-time evaluation and interpretation of data in order to manage risk – and is attributable not just to lack of coordination but also to inadequate IT infrastructure. In the absence of real-time information, there is the temptation to extrapolate from previous epidemics (e.g. FMD) that may actually be dissimilar (e.g. in terms of viral persistence). This weakness may be compounded by the historical

preference of public health systems to rely on epidemiology forecasts rather than engage with the implications of scientific uncertainty.

There is a need for the UK to build more infrastructure to support research across a broad area (because of the uncertain nature of future threats). While the UK might not be able to match the intensity of activity in Hong Kong (influenza epicentre) or the US CDC (response to bioterrorism), it is important that the UK has sufficient infrastructure to capitalise on the expertise currently available – and to prepare the next generation expertise.

Concern was expressed that the Health Protection Agency (HPA) may not recognise the importance of the R&D agenda – assuming that Standard Operating Procedures will suffice to underpin responsiveness – and that too much attention has been devoted to bacterial pathogens (because of food microbiology as a political priority), at the expense of respiratory viruses. There is also continuing need to build research capacity in the regional public health laboratories, so that they do not become dominated by the imperative of service provision. The importance of building research capacity regionally (as well as centrally) reinforces the recommendations in the Academy Report 'Academic Medical Bacteriology in the 21st Century'.

In short, it was concluded, that the UK was lucky – in the low incidence of SARS – but if there had been a crisis, the UK may have struggled to respond in consequence of the weakening of surveillance structures.

Academic support/capacity

It was also concluded that the UK is lucky because of the available coronavirus expertise – but equivalent expertise may not be available "next time", for a different virus, for example a flavivirus (e.g. West Nile and related viruses). There is a need to review expertise in the UK and to ensure coordination of activities such that resources are not wasted on excessive duplication and a fast response can be mounted against new threats. There appears to be no mechanisms for providing funding in an emergency – coronavirus expertise in Bristol was mobilised efficiently to support the HPA, but only through the use of University funds. Such *ad hoc* arrangements do not offer much confidence that the UK will respond effectively to future emergencies. More funding is required to build academic research capacity in pathogen discovery and host specificity – prioritising according to perceived risk but also ensuring cover and response capability. The UK is losing competitiveness in this field and the weakness is exacerbated by unnecessary divisions between human and animal health research (divorced at both funding and policy levels).

Insufficient notice has been taken of the interface between human and animal infectious diseases in allocating priorities for funding; there is a need for more connectivity between the funding bodies in order to encourage and support joint programmes in veterinary and human medicine.

Regulatory issues

There are critical matters relating to both animal research and safety (containment) regulations. For animal research, it could have been difficult to initiate a SARS-primate study rapidly in the UK, if that had been deemed necessary. It is important that the UK raises preparedness by having a generic Home Office project licence in place to enable such research to proceed in the event of a public health imperative.

With regard to the provision of containment facilities, the difference was noted between US practice (primary protection of researcher) and EU practice (physical containment of risk) – international inconsistencies in containment practice should be resolved. In the UK, there is probable need to upgrade facilities (from category 3 to 3+, particularly at the regional level), to identify whether more category 4 facilities are required, to improve funding for running costs and to maintain a cadre of appropriately trained staff. While it seems appropriate for the early research groups (with HSE) to decide on containment status in a novel episode, there is room for clarification of the ACDP role in deciding national status in a timely manner once the organism is characterised.

Horizon scanning

In addition to the issues already described (responsiveness, facilities, research culture), there is also the issue of whether SARS can be perceived as a paradigm for bioterrorism. Does SARS serve as a wake-up call to the EU and the UK to evaluate preparedness? Would increasing preparedness in biodefence help the responsiveness to other new, infectious diseases? If biodefence plans were in place, the UK would not have to rely on luck next time.

Role of industry

Much of the healthcare industry would be dependent on academic research leads in new infectious diseases, and there are issues for facilitating the interface between the sectors. It is unlikely that there are major HPA-spin off company opportunities; it would be easier to commercialise new areas with pre-existing companies, particularly if there is pre-existing hardware to serve as the template. But, for industry to be interested (in developing diagnostic kits, vaccines, therapeutics) there must be sufficient market incentive and, hence, political will to create the incentive.

Conclusions

- Many of the academia/Public Health Laboratory issues raised echo the weaknesses identified in the Academy (2001) Report "Academic Medical Bacteriology in the 21st Century" (that had alluded to significant problems in clinical virology). The report may be downloaded from the Academy web site: http://www.acmedsci.ac.uk/f_pubs.htm
- The issues raised are also highly relevant to current discussions on the programme of the Academy Forum (e.g. role of industry/partnership in response to new and emerging infections/bioterrorism) and specific proposals will be reviewed shortly.

Report of the Meeting held on 13 November 2003

In introducing the agenda of the second meeting of the SARS working group, held on 13 November 2003, the Chairman initially noted that the conclusions from the previous meeting (9 June 2003) were still relevant (discussed further below).

Review of recent developments

Discussion of SARS developments since the last meeting covered: global consensus-seeking (WHO document), biological characterisation, diagnosis, development of animal models, epidemiology, public health controls, and resource issues. Key issues include:

- Diagnostics: PCR-based methods are still problematic (with lack of sensitivity, for example, for upper respiratory tract samples) so there is still no fast diagnostic test for the early stages of SARS.
- Serology: also still insecure because of SARS cross-reactivity with other human coronaviruses.
- Animal models: despite the recent publication of studies on cats and ferrets, there is no reliable model and fast progress cannot be expected if animal studies must be conducted within category 4 containment facilities.
- Molecular biology: good progress is being made (for example in focussing on those proteins not found in other coronaviruses, that might mediate interaction with immunological system), but there is a continuing issue of the lack of UK strategic priority and no extra research funds were made available. To confirm the point made in previous meeting about research, it is important to learn the lesson from the SARS episode so as to identify ways to enable rapid mobilisation of funds in an emergency. It is also important to do more to coordinate and bridge animal and human research agendas (for example, to explore species tropism in zoonoses).
- Vaccine strategy: current initiatives on killed vaccines could not be viewed optimistically in light of the specific experience with other coronaviruses, the general concern that there might be evolution of the virus under selective pressure of vaccination and the practical impediment of current lack of animal model. Scientifically, there may be better prospects for new anti-virals (based on research advances, for example, protease inhibition).
- Epidemiology: while useful information has been collected for SARS – for example, relating to effectiveness of public health measures – it may be difficult to generalise so as to improve preparedness for other infections (because of the unusual features of SARS). It is unfortunate that there has been no commitment to systematic international data collection: there is need for a standardised electronic database on patient information, epidemiological parameters, symptoms, treatments and outcomes.
- Coronavirus research repository: there is also a need for a central resource bank of standardised reagents and sera/isolates, including those from the veterinary side.

Preparing for future events

- Views differ on the probability of SARS returning. The low transmissibility of SARS may put it on the borderline for sustained seasonal occurrence but mutation or the impact of superspreader events may promote recurrence. There are likely to be major co-morbidities, for example the use of high-dose steroids but it is difficult to analyse the evidence in absence of systematic data collation.
- It can be assumed that new infections will become more common globally and that there will be uncertainty about the biological properties during the early stages. This has implications for NHS contingency plans (for example, strategy for isolation hospitals), for the frequency of false positive diagnoses overloading HPA systems, and for the demand to develop locally usable molecular-based diagnostics.
- Confirming the points made in the previous meeting, there is continuing need to provide for and promote, HPA R&D, either by reconsidering the previous reorganisation (that has not been helpful to research) or by better linking to university research. It is necessary to address the current lack of mechanism for incentivising industry R&D for vaccines and anti-virals (in the absence of defined commercial market) and so as to capitalise on the technology that can provide new approaches to diagnostics. One joint approach to these public and private sector R&D weaknesses might involve creating a process to establish an expert group (HPA-academia-industry) to draw on the science in developing new diagnostics in an emergency (by analogy with the Civil Contingency science advisory group).

Priorities for further action

In conclusion, the Academy of Medical Sciences has identified the following issues that require action:

- Making the case for improved HPA research capability to develop sophisticated diagnostic systems for SARS and, more generally, by linking with academia.
- Making the case for Government (OST) to establish a rapidly mobilisable contingency fund (perhaps £10 million) for emerging research priorities created by infectious disease threats.
- Establishing a coronavirus research repository (in London).
- Supporting the proposal for a Euro-CDC, if this improves.
- European/national capacity to react in an emergency and if located near to established public health expertise (preferably the UK).
- Developing integrated international patient information/outcomes database To evaluate therapies widely used to treat SARS patients

The Academy, working with the key agencies and stakeholders, will be taking these issues forward.

Dr Robin Fears and Mr Laurie Smith
December 2003

Appendix 1: Working Group Membership

Professor Tony Minson, FMedSci ***Working Group chair***
Professor of Virology,
University of Cambridge

Professor Roy Anderson, FRS, FMedSci
Professor of Infectious Disease Epidemiology and Head of the Department of Primary Care and Population Health Sciences,
Imperial College London.

Dr Michael Crumpton, CBE, FRS, FMedSci
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Professor Stuart Sidell
Professor of Virology,
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Sir John Skehel, FRS, FMedSci
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Professor Geoffrey Smith, FMedSci
Wellcome Trust Principal Research Fellow & Professor of Virology,
Imperial College London

Dr Maria Zambon
Head of the Respiratory Virus Unit,
Health Protection Agency.

Secretariat was provided by Dr Robin Fears (Senior Policy Advisor to the Academy) and Mr Laurie Smith (Policy Officer for the Academy).