ARTICLE

From malaria and influenza to severe acute respiratory syndrome, Hong Kong has seen more than its fair share of infectious disease. However, in the wake of recent events, research foundations for the rapid identification, containment and control of emerging and re-emerging agents have been laid, as Richard Collins explains.

Out of darkness

Infectious disease research in Hong Kong

In the novel *Heart of Darkness*, author Joseph Conrad's protagonist goes on both a physical journey into the heart of the African wilderness and also a spiritual journey into the soul of man. In a more urbane parallel, Hong Kong too has journeyed from a Victorian plague-infested colonial outpost to a modern metropolis, replete with all the medical conveniences expected of a developed economy.

However, the spectre of severe acute respiratory syndrome (SARS) in 2003 triggered a renewed exercise in soul-searching that began in 1997 with the deadly outbreak of avian influenza H5N1, the first documented direct transmission of a bird-adapted influenza virus to a human. As a consequence, infectious disease research in Hong Kong has increased significantly. The results of that investment are still a long way off, but the implementation is based on strong foundations.

Infectious disease in history

Localised outbreaks of infectious disease have been recorded since Biblical times. For example, two of the 10 plagues recorded in the Old Testament (Exodus) can be attributed to infectious disease. Epidemics of infectious disease have led to the downfall of entire civilisations. The so-called Golden Age of Greece ended around 430 BC when Athens was stricken by an unknown plague carried by rural refugees seeking protection within the city walls from marauding Spartans. Other global pandemics such as the mediaeval Black Death and Spanish Flu in 1918 have been documented extensively.

Infectious disease in Hong Kong

Malaria was endemic in Hong Kong prior to the region's colonisation by the British in the 1840s. The rich moved to the relatively cool and breezy hills of Hong Kong Island to avoid the oppressive humidity, inadvertently removing themselves from the stagnant breeding grounds occupied by the parasite-ridden mosquitoes that were only confirmed as the carriers of the disease in 1897.[1] No such protection was available to the majority of the population, however, and increasing urbanisation, overcrowding, poor sewage and limited access to healthcare created ideal circumstances for repeated outbreaks of malaria, cholera, tuberculosis and smallpox.

While these debilitating diseases have been largely eradicated in Hong Kong and

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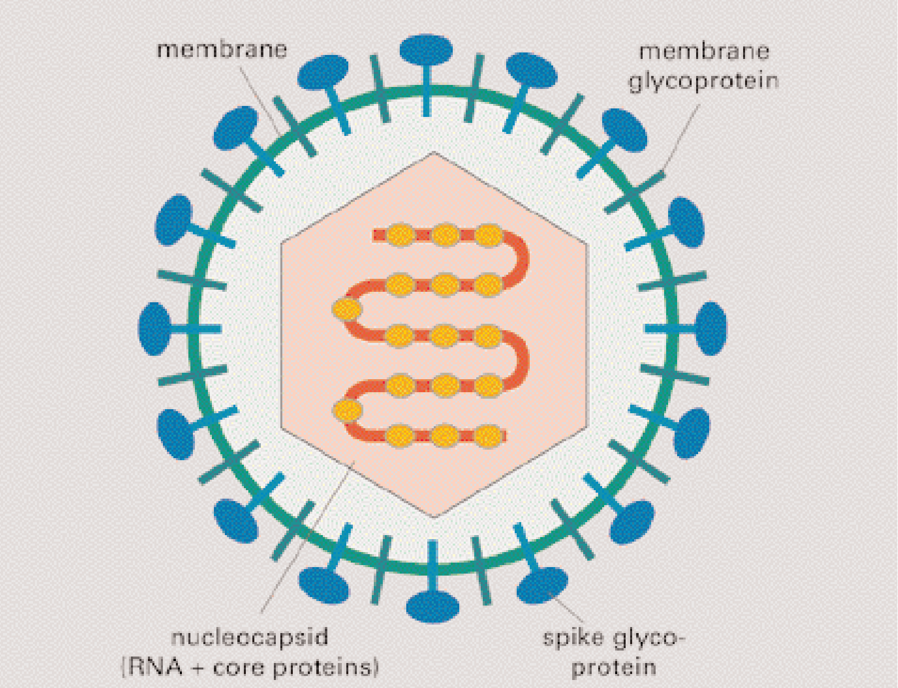

Fig 1. Diagrammatic representation of the SARS coronavirus.

elsewhere around the world, occasional cases of malaria, cholera, rabies and, more recently, dengue fever continue to be reported in Hong Kong.[2] Of greater concern, however, are new, rapidly emerging diseases, of which Hong Kong has had more than its fair share.

H5N1: a new killer emerges

In 1997, a new strain of influenza was isolated from a human patient. An avian influenza A virus known as subtype H5N1, normally found only in domesticated poultry and wild birds, had been shown to directly infect humans.[3] The implications were staggering.

Normally, the cellular tropism for influenza viruses is such that avian-adapted strains cannot pass readily to distantly related species such as humans. The standard model for influenza transmission across species required the presence of a 'mixing vessel' – an intermediate host such as a pig – that is susceptible to simultaneous infection by avian- and human-adapted strains. The segmented genome of the influenza virus allows genetic re-assortment during intracellular virus assembly, making the production of a new avian-human subtype possible. With H5N1, the mixing vessel was no longer required.

The prospect that H5N1 and other highly pathogenic avian influenza A subtypes, such as H7, that are responsible for enormous flock mortality around the world could spread rapidly among the human population with devastating consequences was now very real. The world was on the verge of another global influenza pandemic unseen since 1918, when 20–40 million people are thought to have died from influenza. Only the prompt culling of all poultry in Hong Kong averted further spread to humans. Further territory-wide culls in 2001, 2002 and 2003 to eliminate highly pathogenic avian influenza subtypes underlined the ever-present danger faced by Hong Kong.

Ultimately, only six people died and 12 other known infections were recorded during the 1997 outbreak. Interestingly, follow-up seroepidemiology studies indicated that 3.7% of healthcare workers attending H5N1-infected patients, 3% of government workers contracted to perform the mass poultry cull and 10% of general poultry workers had antibodies to H5N1, indicating that a large group of people had been exposed to the new virus.[4,5] It is expected that similar evidence of spread in the human population will be found following the 2004 outbreak of avian influenza in South-East Asia and other regions.

SARS: another new killer

According to the World Health Organization, the atypical SARS pneumonia infected 8098 people around the world and claimed the lives of 774.[6] In Hong Kong, 1755 people were infected and 299 died. The social impact was enormous, with many people going to work each day wearing facemasks and avoiding public places as much as possible. Schools were closed for weeks, many businesses went bankrupt and the economy suffered greatly.

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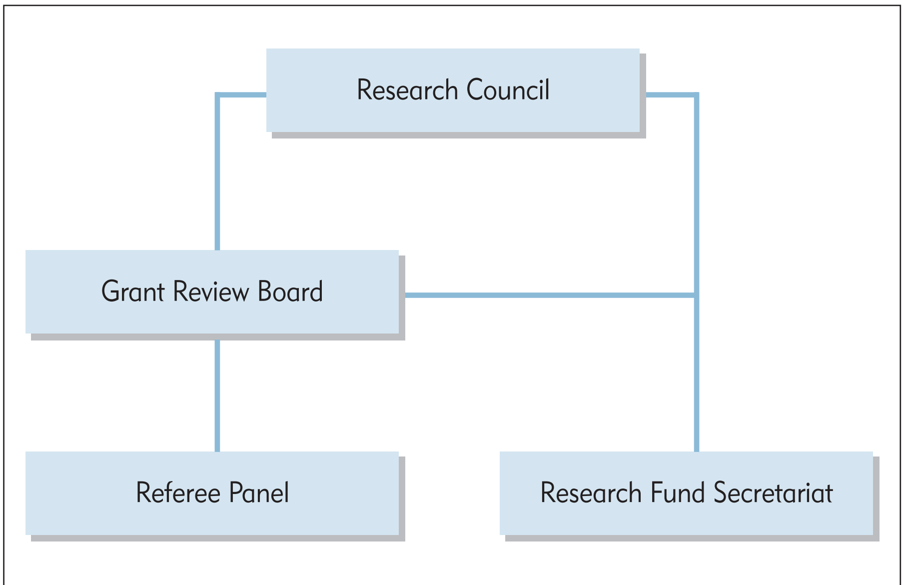

Fig 2. Organisation chart.

The new coronavirus (Fig 1) that caused SARS was isolated and identified in Hong Kong.[7] It was only the third human-specific member of this small group to be discovered since 1965.[8] A fourth, non-pathogenic member, HCoV-NL63, has recently been identified.[9]

It is most likely that the virus was spread by droplet infection in aerosols as many of the initial infections occurred in confined spaces. The now infamous Patient Zero seems likely to have infected several others in a lift or lift lobby in a hotel in Hong Kong. The infected subjects went on to spread the disease to Vietnam, Canada and Singapore.[10]

Another source of infection was between patients and staff in hospitals where nebulisers were used during routine medical procedures.[10] Most disturbingly, a large outbreak in a residential tower block in Hong Kong may have been spread by windborne aerosolised infected material or through the sewage system.[10,11] Indeed, Conrad's image of "death skulking in the air, in the water" seems an apt description of the situation.

Why did SARS become such a devastating illness? The parallels with the 1997 H5N1 influenza outbreak are uncanny. With H5N1, the proximity of humans, pigs and poultry in the largely rural southern China provinces created ideal opportunities for genetic re-assortment of influenza viruses. Similarly, it is speculated that the SARS coronavirus originated in wild animals housed in the unhygienic live animal markets that are common throughout China. This theory was supported by the finding that the first cases of SARS occurred in animal handlers at markets or in people who had eaten wild game or had other contact with such markets.[12]

Furthermore, retrospective seroepidemiological studies indicated a high proportion of wild-game market traders had antibodies to the SARS coronavirus, indicating that they had been exposed routinely to the virus over a long period.[12] A cull of captive wild game and thorough market cleansing were ordered. To date, while some live animal trade is still permitted in China it is highly regulated and a shadow of its former self. These measures, together with the quarantine of exposed patients during treatment and instigation of rigorous hygiene measures in hospitals and clinics, have significantly reduced the threat of a renewed SARS outbreak.

The outbreaks of H5N1 and SARS show both the importance of China as a source of exotic new viruses and also the high probability that zoonoses (human infection with animal pathogens) will occur again under the right circumstances.

Modern infectious disease

The importance of zoonoses is underscored by a host of other newly discovered infectious diseases during the latter half of

Table 1. Breakdown of RFCID applications since inception.

	1ST ROUND	2ND ROUND
No applications received (investigator-initiated)	114	48
No applications approved (investigator-initiated)	25	13
Total amount requested (HK$ million)	111.15	30.33
Total amount approved (HK$ million)	18.73	9.22

Table 2. RFCID grant application grading results.

GRADE	COMMENT
A	Project approved. Funding may proceed immediately.
B	Funding is approved pending clarification of minor issues.
C	Resubmission is required. PI must address serious methodological, logistic and/or financial matters.
D	Application rejected.
E	Out of scope/irrelevant. This has no implication on the quality of the science or the applicant. The application is irrelevant to the stated themes of the fund.

Table 3. Breakdown of RFCID applications by investigating institution (2003–2004).

INVESTIGATING INSTITUTIONS*	NUMBER (%)	
	1ST ROUND	2ND ROUND
Hong Kong only	94 (82.5)	41 (85.4)
Hong Kong + Mainland China	11 (9.6)	3 (6.3)
Hong Kong + overseas	6 (5.3)	3 (6.3)
Hong Kong + Mainland China + overseas	3 (2.6)	1 (2.1)
Total	114 (100)	48 (100)
* Principal applicant must be based in Hong Kong		

‘Hong Kong’s experience of SARS was the catalyst that led to its placing a high priority on both basic and applied science for the control of infectious disease’

the 20th century. Human immunodeficiency virus (HIV) infection is thought to have passed to humans in Africa from infected primates eaten as game (frighteningly similar to the SARS scenario), and the origin of all human strains of HIV-1 has been traced to certain species of chimpanzee.[13] Nipah virus was transmitted from bats to pigs and humans in a large outbreak in Malaysia in 1998 that eventually claimed over 100 lives and devastated the country’s pig rearing industry.[14] Several viruses related to Nipah have also been discovered (eg Hendra virus). Hantaviruses are a family of related viruses that cause hantavirus pulmonary syndrome (HPS). Sin Nombre virus, the leading cause of HPS in the United States, was identified in 1993. This hantavirus is transmitted by the deer mouse, and infection is by inhalation of aerosolised faeces, urine or saliva from the infected animals.[15]

Given the rapid erosion of natural habitats where pathogens co-exist in equilibrium with their respective hosts, it is likely that the number of exotic zoonoses will increase in the near future as man continues to expand into virgin territories and encounter organisms to which he has no natural immunity.

Increased research

The SARS Expert Committee Report was submitted to the government in October 2003.[10] The report made 46 key recommendations to strengthen system capability and preparedness for future outbreaks of communicable diseases. In particular, it indicated that increased research in the following areas was desirable:

- Improved diagnostic techniques
- Clinical management of SARS, including therapeutics and the role of traditional Chinese medicine
- Transmission risks of SARS
- Most appropriate hospital infection control measures for SARS
- Seroprevalance of SARS in defined populations and communities
- Cost and clinical effectiveness of community infection control measures for SARS
- Long-term consequences of SARS.

In July 2003, before the Expert Committee had submitted its report, the Research Fund for the Control of Infectious Diseases (RFCID) was established with a HK$ 500 million (£36 million /€54 million) injection to encourage, facilitate and support research on the prevention, treatment and control of infectious diseases, in particular emerging infectious diseases such as SARS.

Initially, HK$ 50 million (£3.6 million) was transferred directly to the Ministry of Science and Technology of the People’s Republic of China to support research projects on infectious disease on the mainland, with the remainder to be used for pertinent research in Hong Kong-based institutions.

Scope and eligibility

The scope of the RFCID covers four broad areas:

- Aetiology, surveillance, epidemiology and public health
- Basic research
- Clinical and health services research
- Enhancement of research infrastructure.

The RFCID is open to researchers from public, private and academic sectors in Hong Kong; however, collaborating research with mainland China and overseas institutions will also be considered.

The establishment of the RFCID supports investigator-initiated projects (those that encourage the development of innovations from individual researchers) and commissioned projects (those that address specific research needs, fill gaps in scientific knowledge and respond to public health needs and threats).

To date, two commissioned projects involving leading universities in Hong Kong have been approved that span five years and are worth HK$ 55 million. A third commissioned project with a government agency is being considered. For the investigator-initiated projects, 114 completed applications were received during the first open call (closing date November 2003) and 48 during the second open call (closing date February 2004) (Table 1). The third call closes in September 2004.

Grant types

Two types of grant are available under the RFCID. Mini grants are suited to short pilot studies and have a value of HK$ 80,000 (£5700). They should be completed in one year and cannot normally be renewed. In contrast, the upper limit of full grants is

HK$ 800,000 (£57,000). These grants run for two years and may be renewed contingent upon progress.

Peer review

The RFCID is managed by a Research Council (RC), which is advised by a Grant Review Board (GRB) and a panel of local and overseas expert referees. All grant applications undergo a two-tier peer-review process. The RC and GRB are supported by the Research Fund Secretariat (Fig 2).

Grant processing

The Research Fund Secretariat performs an initial review of each application. Those applications that fall outside the scope of the RFCID are removed and requests are made for further details, if necessary (eg figures, reprints of relevant articles, confirmation of ethical approval etc) to complete the application.

As there are several basic, clinical and health research funding agencies in Hong Kong, care must be taken to ensure that research is not double-funded. Consequently, copies of any applications made to other funding bodies and previous reviewers' comments are usually requested for review purposes. After the application is complete, it is sent to one or two overseas reviewers. The HWFB maintains a database of local and overseas experts (identified from professional contacts and recommendations and by review of relevant literature, news and current events in science).

Owing to the small size of the research community in Hong Kong, local reviewers receive anonymised copies of the application in which all references to the identity of the applicants and their institution are removed to reduce bias. After potential reviewers are identified they are sent an invitation and an abstract of the application, together with the terms and conditions of the review, by email. Upon acceptance, the entire application and reviewers' notes are sent by courier. We generally allow four to six weeks for reviewers to respond. All overseas reviewers receive a small honorarium for each review they complete.

About a month after the closing date the GRB sits to consider the applications. At present, the GRB comprises a pool of about 40 individuals, mainly university professors in the clinical and basic science fields, senior hospital consultants and senior executives from appropriate government departments (eg Department of Health and the Hospital Authority). At any one time, only about a dozen are available for GRB duties. After the GRB reviews are collated and compiled, the Research Council – a select committee of academics and senior government staff headed by the Secretary for Health, Welfare and Food – endorses the rating of each application. The Research Council decision is final. Immediately following the Research Council meeting the results of the review process are sent to the applicants. Results are graded A-E (Table 2). The total time between the deadline for receipt of applications and issuing a decision letter is 17–22 weeks.

While the RFCID is principally for use by Hong Kong-based researchers, the value of collaboration, both with mainland China and with overseas institutions, is recognised. However, the number of collaborations has not changed significantly during the time the fund has been open to applications (Table 3). This may be because the RFCID is a new fund and its existence to overseas institutions is not widely known. Collaboration between institutions, particularly with those based in mainland China, improves the technical skills and reputation of scientists and institutions by exposure to international expertise.

Into the light

More than any other event in its long history of tackling infectious diseases, Hong Kong's experience of SARS was the catalyst that led to its placing a high priority on both basic and applied science for the control of infectious disease. The foundations for the rapid identification, containment and control of emerging and re-emerging infectious disease have been laid. Finally, Hong Kong is emerging out of the darkness.

Details of the Research Fund for the Control of Infectious Diseases and other grants administered by the Health, Welfare and Food Bureau can be obtained from the bureau's webpage (http://www.hwfb.gov.hk/grants). ■

REFERENCES

1 Ross R. On some peculiar pigmented cells found in two mosquitoes fed on malarial blood. *BMJ* 1897; **2**: 1786–8.
2 Auyeung TW, Que TL, Lam KS, Ng HL, Szeto ML. The first patient with locally acquired dengue fever in Hong Kong. *Hong Kong Med J* 2003; **9**:127–9.
3 Subbarao K, Klimov A, Katz J *et al*. Characterization of an avian influenza A (H5N1) virus isolated from a child with a fatal respiratory illness. *Science* 1998; **279**: 393–6.
4 Bridges CB, Lim W, Hu-Primmer J *et al*. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997–1998. *J Infect Dis* 2002; **185**: 1005–10.
5 Buxton Bridges C, Katz JM, Seto WH *et al*. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. *J Infect Dis* 2000; **181**: 344–8.
6 WHO. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003 (revised 26 September 2003). www.who.int/csr/sars/country/table2003_09_23/en/ (accessed 20 April 2004).
7 Peiris JS, Lai ST, Poon LL *et al*. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; **361**: 1319–25.
8 Tyrrell DA, Bynoe ML. Cultivation of a novel type of common cold virus in organ cultures. *BMJ* 1965; **5448**: 1467–70.
9 Van Der Hoek L, Pyrc K, Jebbink MF *et al*. Identification of a new human coronavirus. *Nat Med* 2004; **10**: 368–73.
10 SARS Expert Committee Report. *SARS in Hong Kong: From Experience to Action.*
11 Yu IT, Li Y, Wong TW *et al*. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *N Engl J Med* 2004; **350**: 1731–9.
12 Guan Y, Zheng BJ, He YQ *et al*. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 2003: **302**: 276–8.
13 Gao F, Bailes E, Robertson DL *et al*. Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. *Nature* 1999; **397**: 436–41.
14 Chua KB. Nipah virus outbreak in Malaysia. *J Clin Virol* 2003; **26**: 265–75.
15 Mills JN, Corneli A, Young JC, Garrison LE, Khan AS, Ksiazek TG. Hantavirus pulmonary syndrome. United States: updated recommendations for risk reduction. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2002; **51**: 1–12.

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