Chapter 10

EMERGING INFECTIOUS DISEASE RESEARCH IN CANADA – Lessons from SARS

The Canadian experience with SARS reminds us that the investigation of an epidemic is research—research conducted at a feverish pace. Chapter 5 outlined how the research conducted during an outbreak is essential to effective response measures and ultimate control of the epidemic. Unfortunately, with a few notable exceptions, Canadian governments and public health institutions did not heed the warnings of the 1994 Lac Tremblant declaration and build the necessary research capacity for emerging infectious diseases. Research and evaluative capacity in public health more generally was not sustained during the budget roll-backs of the 1990s, as deficit-cutting reductions in federal transfers limited provincial and municipal spending.

A more fundamental problem, however, is one of culture and commitment. Quebec's National Institute of Public Health and the British Columbia Centre for Disease Control [BC CDC] have supported research, and Health Canada's realignment in 2000 provided tangible support for in-house science capacity. However, the Committee perceives that public health agencies and governments have often regarded research capacity as academic, irrelevant, and discretionary rather than the core public health function that it is. F/P/T governments have significantly increased health research funding across Canada in recent years, but the absolute levels of investment have favoured either investigator-initiated fundamental research or R&D activities that are amenable to short-term economic pay-offs through private partnerships. The Committee strongly supports ongoing and greater investments in "curiosity-driven" research; as discussed below, critical capacity for epidemiologic investigation and outbreak response is built in part by nurturing the related and fundamental science. Similarly, we recognize that the private sector is not only a major investor in research but plays the key role in commercializing beneficial discoveries made with public sector support. However, these types of investments are not aligned with the unique modalities of research and evaluation that are embedded in core public health functions.

A related challenge is the profoundly multidisciplinary nature of effective research targeting an outbreak or epidemic. Many disciplines are needed: e.g., epidemiology, biostatistics, mathematics, medical microbiology, clinical medicine, laboratory science, health systems research, social sciences, and health policy. All must be engaged for the response to be optimally effective. For example, our review of the SARS outbreak in Canada has already illustrated how the ability to do etiologic or diagnostic research requires good epidemiologic and clinical data along with laboratory research capacity. A shortfall in one dimension cannot be covered by strength in another.

The need to value and support a research culture in public health arises from more than its positive impact on our ability to understand and control outbreaks of infectious disease; our standing in research affects how other nations see Canada and its public health system. Science—a system for solving problems and addressing unknowns—is the organizing principle for outbreak management and epidemic response. If other nations lose confidence in the scientific capacity and leadership in our public health system, it can have a lasting negative effect on how other countries choose to interact with Canada, be it through tourism, trade, academic and cultural exchanges, or through multilateral bodies such as the World Health Organization [WHO]. Last, beyond research and evaluation focused on infectious diseases, public health must have a strong scientific foundation and a capacity for critical self-evaluation through generation and application of evidence-based programming.

10A. Emerging Infectious Disease Research: A First Look at the Canadian Record on SARS

Experience with other emerging infectious diseases—HIV, Hepatitis C and West Nile virus, to name but three—has long since highlighted deficiencies in how Canadian research is organized to respond to emergency situations and significant new infectious disease threats. Many experts believe that a slow and poorly-coordinated research response had an adverse effect on Canada's measures to control HIV and Hepatitis C, with resulting adverse impacts on the health of Canadians and enormous direct and indirect costs. With West Nile virus, we have not as yet been able to generate a clear epidemiologic picture of the extent of the problem in humans and the severity of health risks involved. The seasonal nature of the disease means that research capacity must be poised and ready to respond as cases appear. Our current levels and modes of organizing and funding public health research make this difficult.

Earlier chapters have already indicated that the research response to SARS in Canada was uneven: some aspects were performed well; others were not. Research into the cause of SARS, the characterization of the agent, the development of diagnostic tests, and generation of initial clinical descriptions were all conducted and communicated relatively rapidly. Research on the immune response with the goal of developing a SARS coronavirus vaccine has progressed well. On the other hand, research on many fundamental epidemiologic aspects of SARS, including research on the spectrum of disease and such questions as the duration of viral shedding and the period of infectivity, has lacked cohesion. Even now we remain unable to address many of these questions. As a developed country with an acclaimed health care system, Canada has no excuse for its inability to develop an epidemiologic analysis of SARS. The Canadian performance, as already indicated in Chapter 2, contrasts sharply with Hong Kong. Scientists in Hong Kong were able to produce seminal epidemiologic and clinical descriptions while responding to a larger epidemic than Canada faced. Our incapacity arose in part from previously-identified issues of leadership, coordination, data collection and management, data sharing, and weak mechanisms to link epidemiologic and clinical to laboratory data. It also reflects lack of research capacity and advanced planning.

The Canadian research response to SARS as of early August is summarized in Table 1. The issues listed under each type of research are a non-exhaustive summary of the research questions that needed answers. At first glance, the performance appears reasonable. However, these research activities arguably address only a minimal and essential set of issues. Our preparedness for the next respiratory virus season, when SARS could reappear insidiously amidst thousands of Canadians with cough and fever of a more benign nature, would be enhanced by garnering answers to many other questions.

In Table 2, the Canadian performance is compared to the international research response. Again, this assessment was compiled to the end of July 2003. Although other valuable publications have since appeared, this is a context where timeliness of research is critical. The numbers of publications and the impact factor of publications are detailed. The impact factor is one measure, albeit decidedly imperfect, of the uptake of scientific publications. It tallies how often on average papers are cited when published in the journal in question. High-quality and more topical papers tend to be published in higher-impact journals, such as *Science, Nature*, the *Journal of the American Medical Association*, the *New England Journal of Medicine*, *The Lancet*, and the *British Medical Journal*. Although Canada has contributed 20% of the published world literature on SARS, many of these publications are in journals with low impact—they have limited influence on thinking and global knowledge. In addition, there is double counting of reports that were published simultaneously in the Canada Diseases Weekly Report and the US Morbidity and Mortality Weekly Report. Overall, the impact of Canadian research ranked ahead only of China, notwithstanding the fact the indexing services do not list Chinese language publications and they were accordingly assigned an arbitrary weight approximating zero.

The weakness in some areas may speak to the importance of interdisciplinary linkages as highlighted earlier. We noted, for example, that the performance in some aspects of diagnostic work was undercut by weaknesses in collecting epidemiologic and clinical data and integrating these data with laboratory work. The weak performance in research on pathogenesis may be a result of Canada's failure to develop a large cadre of clinician scientists, the fact that some clinician-scientists who had a direct opportunity to study SARS were utterly consumed with managing clinical aspects of the outbreak, and inadequate linkages between clinicians and basic scientists. We turn next to a brief comparison of the research response to SARS with what could or should have been done.

TABLE 1

A Preliminary Summary of the Canadian Research response to SARS as of early August 2003

Type of research	Issues Addressed	Canadian Performance*	Enabling or Limiting Factors
Emergent Research			
Epidemiology and public health	• Incubation period • Attack rates • Routes of transmission • Mortality rates • Infection control issues • Effectiveness of quarantine, travel advisories, passenger screening	++ ++ +++ ++ +++ +	Problems in data management and sharing, as well as poor linkage of laboratory and epidemiologic data, limited and are still limiting our ability to do these types of studies.
Etiologic and Diagnostic	• Identification of causative agent. • Most appropriate specimens source and timing. • Sensitivity, specificity of different diagnostic tests	+++ + +	Work was complicated by changing case definitions, changing classification of cases and limited integration of clinical and epidemiologic data with laboratory data.
Clinical	• Spectrum of disease • Clinical manifestations • Therapy of disease • Long term sequelae	++ +++ + +	An initial clinical descriptive paper was published, plus an analysis of critically ill patients; but little work on other aspects thus far.
Pathogenesis	• Mechanisms of disease causation • Animal models • Genetics of susceptibility to disease	++ +++ ++	Some opportunities lost because of slowness to engage basic scientists or limited number of clinician scientists. More opportunities remain unexploited.
Virology	• Basic biology • Genome sequencing • Protein characterization	– +++ +++	Existing collaborative networks facilitated genome and protein work.
Immunobiology	• Correlates of protective immunity • Vaccine development	++ ++	These studies are underway.
Post Event Research			
Health Systems Research	• Cost effectiveness of interventions • Unintended consequences of interventions • General Health Economics	+ + +	The type of research is not essential early in the epidemic response and is appropriately commencing now. However, the lack of linked and comprehensive data will impede the quality of these studies for some time.
Social and economic	• Individual impacts of the epidemic and interventions. • Behavioural research • Societal impacts of the epidemic and interventions	+ + +	CIHR has a future competition planned in these areas.
Policy	• Lessons learned • Public health implications	++ ++	These are currently in progress.

* +++ Indicates Canadian scientists completed research on the issue, which has been communicated scientifically as well as publicly. For most sub-categories of emergent research, this would be considered an adequate or better response.

++ Indicates research work is in progress.

+ Indicates research projects are being planned.

– Indicates no current work in progress or that there is no longer the ability to do the work.

TABLE 2

Numbers and Impact Ranking of Canadian SARS Research Reports as of Early August, 2003

		Canada	United States	Hong Kong	China	United Kingdom	Singapore
Epidemiology and Public Health	Publications	6	2	3	10	2	2
	Mean Impact Factor	3.4	15.0	16.3	0.1	18.0	0.0
Etiology and Diagnostic	Publications		2	2	2		
	Mean Impact Factor		15.0	9.0	0.0		
Clinical	Publications	8	2	13	15		6
	Mean Impact Factor	10.5	6.5	10.1	0.3		4.5
Virology	Publications	2	1	3	9		1
	Mean Impact Factor	11.5	23.3	17.5	0.2		13.3
Immunobiology	Publications				4		
	Mean Impact Factor				0.6		
Social and Economic	Publications	7	1			1	
	Mean Impact Factor	1.3	23.3			0.8	
Policy	Publications	1				1	
	Mean Impact Factor	13.3				6.6	
Totals		24	8	21	40	4	9
Percent		20.5	6.8	17.9	34.2	3.4	7.7
Impact Factors/ Publication		5.9	14.9	11.4	0.4	11.0	21.7

* Impact was calculated by averaging the 2001 Institute for Scientific Information [ISI] impact ranking of journals in which a given country's research was published. The analysis is based on publications listed in the US National Library of Medicine as of July 30, 2003. Journals for which the ISI has no impact factor ranking, such as Chinese language publications and the Morbidity and Mortality Weekly Report [MMWR] and the Canada Diseases Weekly Report [CDWR] were given an impact factor of 0.001 in calculating means.

10B. Outbreak Investigations and Research

Chapter 5 outlined how outbreak investigations and research interconnect. The research response to an epidemic such as SARS has several phases, including the identification, characterization, response, monitoring and post-event phases. Ideally clinical, epidemiologic, laboratory and social science research tools are used in an integrated and coordinated fashion in each phase. These phases are not entirely sequential. Each phase of the research response brings different questions and thus the required research response may be different in terms of resources or expertise. Functionally in Canada, each phase had and has different mechanisms for leadership, direction, organization, and funding. Some aspects of research are required for emergency response, while others are better suited to answering longer-term questions of equal import but less urgency.

In the identification phase the questions are: What are the manifestations of infection? What is causing the outbreak or epidemic? How is the causative agent transmitted? When does transmission occur? The cause of any epidemic is not known when cases first begin occurring. An epidemic caused by a known agent usually requires, in the initial identification phase, competent

public health laboratories to test for known agents, in addition to epidemiologic and clinical research resources. An epidemic caused by a new agent, such as SARS, requires more robust laboratory research capacity. The SARS coronavirus was identified quickly with traditional technology. Advanced proteomics, genomic and genetic technologies were employed after identification to characterize the agent; such technologies may have been needed in the first instance to identify a more fastidious organism. Fortunately, these capacities were in place and operational well before an event such as SARS: Canada has considerable strengths in multiple academic centres in genomics and proteomics, and the National Microbiology Laboratory [NML] fulfilled its function appropriately as a national reference laboratory. These responses also depended on existing collaborative relationships. For the future, Canada should develop and sustain a strong national network of fundamental and applied scientists capable of rapid research responses to the next outbreak of a novel infectious agent within our borders.

In the characterization phase, research turns to the development of diagnostic tests, determining the spectrum of disease, assessing the extent of infection, and delineating the mechanisms of disease pathogenesis. We now have effective diagnostic tools in Canada. Indeed, multiple sites have been active in developing and enhancing SARS-specific diagnostic technologies. However, the Canadian research response has yet to generate meaningful data on the spectrum of disease, the extent of infection, and understanding of mechanisms of disease pathogenesis. The international public health community was looking to Canada for answers to questions of global significance, and our response was inadequate.

Bringing an epidemic under control requires effective public health and clinical action. Research on the response to an epidemic is important to understanding the effectiveness of interventions and refining or abandoning them. The interventions used in the response to SARS—antiviral treatment, quarantine and isolation, suspension and redirection of hospital activity, travel advisories, screening of travelers—all were employed empirically. Adverse effects ranged from direct drug toxicity for patients treated with antiviral drugs, to loss of income and psychosocial consequences for those in quarantine. At a macro-level, the consequences ranged from modest inconveniences (longer airport lineups) to very serious health threats (delayed health services) for hundreds of thousands. There were also national economic impacts that affected millions of Canadians. There were and still are few data on which to base judgements about the relative benefits of any of these interventions.

Some caused adverse effects without any benefit. For example, during SARS there was a laudable attempt to conduct an emergency clinical trial of ribavirin. However, before this could be mobilized, ribavirin became the "standard of care" for SARS and a trial was no longer thought to be "ethical". Unfortunately, ribavirin use in SARS patients had a high rate of adverse events. Later in vitro research showed no activity of the drug on the SARS coronavirus. The suspension of elective services in hospitals and quarantining of thousands of individuals, as occurred in Ontario, had obvious adverse impacts.

All these decisions were made in the face of crisis conditions and the pressing need to contain a serious outbreak. Careful evaluation of the effectiveness of the relevant public health and clinical measures should not imply any adverse verdict on the judgement of those who used them. Science progresses by turning today's truths into tomorrow's mistakes. Evaluation in hindsight is always easier than decision making under duress. But that is all the more reason why evaluation should occur to inform future decision making. It needs to be conducted now, so that potential future epidemics can be dealt with using interventions with the least unintended negative effects.

Finally, passenger screening was implemented at substantial cost to the public health system and travel advisories were issued with severe economic effects. In the end, were there any positive health effects from these measures? We need to know their impact with certainty and communicate the results.

Monitoring the effectiveness of response through enhanced surveillance becomes important as an outbreak comes under control. This is the phase of research we are in now. As already noted, enhanced surveillance will be extremely important nationally and for other jurisdictions in the northern hemisphere as we enter the next respiratory virus season.

Once an epidemic is over, various types of post-event research can be undertaken. The biomedical, clinical, epidemiologic and public health research activities initiated during the initial phases of outbreak response must be moved to completion. For SARS, there is a continuing need for more long-term fundamental research into the basic biology of the virus, with a view to designing more effective therapies and developing a vaccine. "Lessons-learned exercises" are another type of evaluative research focused on system improvement. This report is an example of one such exercise. Parallel work for Ontario

is underway with the Walker Panel and Campbell Investigation; an expert panel chaired by Prof. Sian Griffiths and Sir Cyril Chantler of the UK is similarly providing a third-party assessment of the SARS outbreak response in Hong Kong.

Assessing the long-term sequelae of SARS and its overall health impacts are some of the other types of research that are required. Many questions remain unanswered. Do patients affected with SARS all recover full respiratory function? How many patients and health care workers suffered lasting psychosocial harms? What exactly was the economic impact of SARS on institutions and the various segments of the Canadian economy? In this *post hoc* phase of research, more usual research processes may be appropriate.

10C. Reflections on the Research Response to Epidemics

10C.1 Business as Usual

Canada has generally produced research on emerging infectious diseases through the academic model. That is, research is initiated and carried out by one or a few investigators who have an interest in a question; it is funded through peer review, and communicated through peer-reviewed channels. These normal processes for planning, approving, funding, conducting, analyzing and communicating research are ill-suited to meet the early research needs of an epidemic response. Changes must be made during an epidemic investigation, just as changes in the health system's hierarchical structures must be made for effective outbreak management.

Peer review, of course, remains the overall gold standard for what science is performed and where it is published (and thus noticed). Peer review has its failings and critics; however, to paraphrase a similar tag about democracy, it is the worst system for assessing science—except all the others. The basis for this system is to ensure that the highest quality, most important research is performed and that it is verified by other scientists. During an epidemic, the necessity of timely response means that formal peer review is not practicable. This does not mean that quality should be sacrificed. High quality science in the course of an epidemic can be assured by having teams of scientists who are normally full participants in the peer-reviewed processes—competitive granting and publishing in peer-reviewed journals—in place to respond to emergency research needs. Furthermore, this team must have processes for dynamic interchange and critical evaluation of each other's ideas on a rapid timeline. In short, strong leadership by excellent scientists, coupled with internal and external informal peer discussions of experiments and findings, can ensure that emergency work remains high quality.

10C.2 Mobilization of Scientific Resources

In order for scientific resources to be mobilized, they need to exist and be organized in a fashion that permits rapid (less than a day) deployment. Canada needs a cadre of cutting-edge scientists in the public health, clinical, and biological spheres of infectious diseases, who can and will drop everything on short notice and apply their skills to the solution of the health threat at hand. To be cutting-edge and prepared, they must be actively engaged in research and part of the overall Canadian research community on a continuing basis.

This in part is a key role for government science. Strategic investments in government public health science capacity—such as the NML and the BC CDC—were important factors in Canada's ability to respond to SARS. However, networks based in academe and the private sector are also needed to broaden and deepen our response capacity. These research networks cannot be about subsidizing "business as usual", or providing retainers to purchase the goodwill of a set of academics in hopes that they may elect to help out in a national emergency. Funds should flow to build specific capacities and establish delineated obligations—such an apparatus must be established in advance with clear ground rules. Hospitals and universities are useful partners, but the primary connections must be with individual scientists who want to be part of a research response team. Furthermore, epidemic research needs to be organized so that it can react in any or several areas of the country at a given time, and provision must also be made for urgently mobilizing scientific resources from outside the health sector.

The US Centers for Disease Control and Prevention [CDC], for example, co-opted US coronavirus experts shortly after the virus was linked to SARS. Similarly, in the laboratory investigation of SARS, the NML linked to academic institutions, provincial agencies and the private sector. This resulted in the first full-length genome sequencing of the SARS coronavirus by a collaborative team from the Michael Smith Genome Sciences Center, the BC CDC, and the NML. Government investment in basic science capacity over the last several years created research strength that could be drawn into action. However, the timely assembly of such collaborations can only occur if there is already a degree of connectedness,

trust and scientific respect. The middle of an epidemic is not the time to be establishing new linkages and collaborations.

Overall, the SARS experience argues that capacity for cutting-edge science in government is needed, and it needs to be fully connected to and integrated with academic and private sectors through interchanges, joint appointments, collaborations and formal and informal networks. Fostering these linkages should be an integral part of the workplan for a new Canadian Agency for Public Health and the F/P/T Network for Communicable Disease Control. The network should give special priority to linking research in government and academic institutions with a focus on infectious diseases, thereby building the teams and business processes for rapid epidemic investigation that will strengthen Canada's ability to respond to the 'next SARS'.

While some aspects of laboratory research on SARS in Canada were a source of national pride, we have already outlined that more could have been done. Reports on interim laboratory results were not produced and communicated as often as they could have been. Effective linkage of laboratory research at the national level to the clinical and epidemiologic research efforts at the provincial and local level never really happened. Academic linkages tended to be geographically limited.

Mobilization of epidemiologic and public health research was particularly weak. As noted earlier, the research capacity in provincial public health agencies varies, but with some exceptions, is very limited. Indeed, little scientific capacity exists in most local and provincial agencies. The Committee sees an acute need for stronger academic linkages and in-house research capacity for public health agencies at the provincial/territorial level and in major municipalities. Supporting such linkages and capacity should be a funding priority in the transfer programs from the Canadian Agency for Public Health.

Health Canada's capacity in these areas is also limited. The Centre for Infectious Disease Prevention and Control, the main part of the Population and Public Health Branch responsible for surveillance and epidemiologic research on infectious disease, employs only 12 medical epidemiologists and public health practitioners and 9 PhD epidemiologists. Their research productivity varies in part because of competing demands on their time, and in part because the current structures do not lend themselves to academic partnerships.

Connections between the academic sectors in epidemiology and public health and local, provincial and national counterparts have in some cases been eroded. The expiry of initiatives such as Public Health Research Education and Development [PHRED] in Ontario has resulted in the collapse of teaching public health units. As a result, in Toronto during the height of the epidemic, the academic public health sector was not drawn into needed epidemic research, and as yet has produced very little research in these areas. To pick up a theme from Chapter 7, public health units and public health practitioners in major centres need to be integrated into the academic sector in much the same way that teaching hospitals partner with universities and community colleges. The cross-fertilization will improve training opportunities, create more varied and attractive career paths, build a strong research culture in public health, and facilitate the rapid emergence of teams of investigators who can participate in epidemic investigation.

In the latter stages of the SARS outbreak, large research coalitions did begin to emerge in Canada. These include the SARS Research Network in Toronto and the SARS Accelerated Vaccine Initiative in British Columbia. The Canadian SARS Research Consortium was initiated in late May 2003 to "coordinate, promote and support SARS research in Canada and develop international linkages and partnerships to control and eradicate SARS." The consortium was catalyzed by the Canadian Institutes of Health Research [CIHR] to deal with the immediate threat posed by SARS. If it proves successful, the Canadian SARS Research Consortium could become a model and evolve into a more permanent structure to address newly emerging infectious diseases in Canada. The funding partners include the CIHR, Genome Canada, Health Canada, GlaxoSmithKline, the Michael Smith Foundation for Health Research, the Ontario Research & Development Challenge Fund [ORDCF], Fonds de la recherche en santé du Quebéc [FRSQ], the Protein Engineering Network of Centres of Excellence [PENCE], and CANVAC (the Canadian Network for Vaccines and Immunotherapeutics). The Consortium intends to work in diverse areas, such as diagnostics, vaccine development, therapeutics, epidemiology, databases, public health and community impact.

10C.3 Leadership, Organization, and Direction of Research

The usual consensus-building processes for scientific collaboration are difficult to follow in the face of an outbreak and the required research response. Furthermore, assuming that F/P/T public health research capacity is created within public agencies and institutions, jurisdictional tensions could still emerge and impede the research

response to the next major outbreak. These concerns suggest the need for clarity about scientific and research leadership in epidemic research responses.

This is not a straightforward matter. Researchers are not often skilled in management. Moreover, management skills are necessary but not sufficient for the discharge of a leadership role in a crisis. Attempted research leadership also sometimes runs afoul of research 'followership', i.e., researchers resist being organized and steered at the best of times. They have a healthy scepticism about authority, and highly-specialized expertise that is unlikely to be matched by a particular leader. Leadership of a scientific team accordingly derives from competence, respect, interpersonal and communication skills, and mutual trust as much as it does from the authority given to someone in a particular position. This is doubly so when the scientific team is a network of individuals outside a hierarchical organization, in which participants have the latitude to choose their collaborators and their research foci. Furthermore, decisions need to be made in a timeframe that may not allow consensus building.

During the SARS epidemic, effective overall leadership on research was lacking, particularly in the epidemiology and public health sphere. Multiple public health units were involved but coordination was limited and staff were consumed with fighting the outbreak. The provincial public health branch did not have sufficient in-house research capacity or highly-developed academic linkages. As noted in Chapter 2, scientific firepower was marshalled in an advisory committee to support the executive team that oversaw the provincial emergency in Ontario, but this group did not have the time, data, or clear mandate to coordinate the relevant epidemic research. In future, research leadership for outbreak investigation must be determined well in advance, along with a tentative set of managerial structures to move a research agenda forward.

One such structure, as noted earlier, is the creation of a connection between the outbreak management team and the research response team—a B-Team as pioneered by the CDC. This would be a group whose task it was to think critically about the scientific questions, generate ideas for research, and offer sober second thoughts on the overall direction of an outbreak response.

More generally, the research structures themselves need not mirror the command-and-control apparatus needed for effective management of the outbreak per se; but they will be more hierarchical than normal in research. Put another way, the scientific team must have a quarterback and a play book that all will use, albeit temporarily until post-event research brings the more free-flowing processes of normal science on stream.

Those normal scientific processes involve redundancy, repetition and uncoordinated replication, and competition. These processes, with their centripetal tendencies and creative anarchy, have paid huge dividends for society. However, they are too slow, unpredictable, and expensive for outbreak research. This underscores the need, outlined earlier, for two synergistic elements in the research response: a strong scientific presence in publicly-managed and -accountable institutions, and funds flowing through structures that draw non-governmental partners into a network with a clear set of research responsibilities.

For example, in the early stages of the SARS outbreak, laboratory research was relatively well-coordinated because it was centralized. As the health care and academic sectors became engaged and testing for the coronavirus became more widely available, laboratory activity became more fragmented. The ability to track laboratory results disappeared. Central data management was not maintained. Indeed, although many stakeholders called for action, it was not clear who, if anyone, had the authority to insist on better coordination of data management.

The epidemiologic, clinical, public health and social science research efforts were even more fragmented. Health Canada attempted to direct some of the epidemiologic and public health research by developing research protocols and providing funding and direct support. However, progress has been frustratingly slow. The CIHR demonstrated substantial agility and provided some welcome leadership through a special SARS competition, in May. However, some of the individuals who were best placed to address the central questions were already deeply engaged in fighting the outbreak and hardly in a position to write elegant grant applications. An accelerated granting competition may be worthwhile for slower-moving outbreaks or for rapid post-event research, but was criticized by a number of informants as misplaced in the midst of continuing efforts to contain a fast-moving outbreak such as SARS.

Some mechanism for ongoing coordination of SARS research is still needed, as pressing questions remain unanswered. The Canadian SARS Research Consortium and the SARS Accelerated Vaccine Initiative are two examples of efforts to coordinate the research effort. However, these coordinating bodies are operating under no particular authority, and a wide range of other activity is now underway without formal cross-linkages, networking, or coordination. Research on the development of diagnostic tests is illustrative. Diagnostic research can only be done if there is access to clinical specimens. These are only available in any quantity in a few institutions that

may or may not be interested and willing to provide them to researchers. The amount of material is limited so that not every demand for material can be met.

There are also serious organizational and ethical issues in how diagnostic specimens can be drawn into a coordinated research effort. Some researchers have suggested that Canada create a national SARS database to facilitate research, pulling together relevant clinical, epidemiologic, laboratory, and, where applicable, pathological data. This would be novel and ideal. However, individual researchers do not have control over data that accumulate during the response to an outbreak. The data are now held in many different institutions and agencies; they are subject to constraints of confidentiality arising from their acquisition as part of a local public health investigation or clinical encounter.

As well, in usual circumstances, those who generate data "own" the data and decide what is to be done with them. These researchers are under no obligation, except perhaps a moral one, to make data available to others who may be able to use it better. The same applies to biologic materials. These practices must change during provincial and national emergencies, and perhaps more generally.

Thus, a fundamental question that Canada needs to answer is: Who "owns" the various streams of precious scientific data that emerge during an outbreak? During the Health Canada SARS conference in Toronto on April 30/May 1, 2003, it was suggested that the idea of "ownership" of data during an outbreak should be permanently replaced by "stewardship". Operationalizing this idea will be challenging, but is worthy of pursuit.

As a corollary, how can the confidentiality of the affected patients and their contacts be safeguarded in any data amalgamation process? Some informants believe that confidentiality and privacy concerns can be readily managed by having each group or institution in a data stewardship consortium agree on a protocol for "anonymizing" the data, and then using common non-nominal identifiers to create the means for linking data from multiple sources. On the other hand, we noted in Chapter 9 that the *Privacy Act* and *The Personal Information Protection and Electronic Documents Act* and related provincial laws are not well suited to disease surveillance, outbreak investigation, and applied research in the face of infectious diseases. In this regard, an epidemic caused by a new agent presents some unique issues. In broad brushstrokes, the US approach has been to consider public health investigations somewhat differently than planned research activity with respect to some of these ethical issues. More thinking about the ethical and legal dimensions of public health research and outbreak investigation is needed. The rights of the individual must be balanced against the public good of disease surveillance and epidemic research that will safeguard the population's health.

In sum, for future emerging infectious disease threats, some process for coordinating the research effort nationally needs to be in place. A restructured national public health system should have this role, along with the authorities to direct and coordinate research, establish national databases and research platforms, ensure that appropriate ethical and privacy safeguards are in place, and provide resources to fund epidemic response research.

10C.4 Funding

We have already seen that the usual peer-reviewed mechanisms for funding research are not suited to the immediate initial phases of epidemic research. Certain research activities must be carried out regardless of flaws in study design. An outbreak is not the time to allow "the best to become the enemy of the good"; a response must occur. The initial funding for research conducted on SARS was not peer-reviewed in the formal sense and was provided entirely by affected health care institutions or directly by governments. The quality of the work was ensured by pre-existing capacity and networks of scientists who provided real-time informal peer review. Subsequently, the peer-reviewed granting agencies responded to SARS research needs and began funding SARS research in a relatively rapid timeframe. However, at this point we have largely lost the ability to perform clinical research on the pathogenesis of SARS.[1]

It appears that the CIHR was able to hold an accelerated competition in part because of a quirk in their finances for fiscal year 2003-2004. The CIHR and other agencies need to have the capacity to respond to new threats rapidly through the creation of special funding envelopes. It is surprising that the Canadian Food Inspection Agency [CFIA], as an agency with a legislative mandate similar to the CIHR, is able to roll funds over on a 24-month basis while the CIHR is not. Extending this administrative policy to CIHR would clearly improve the CIHR's flexibility in responding to emerging infectious diseases and other fast-breaking research issues.

1 It is arguable that, funding aside, pathogenetic research was impeded by a dearth of clinician scientists and the pressures they were under in fighting the outbreak.

Canada's investment in infectious disease research and special funding for SARS is detailed in Table 3. To date, the Government of Canada has invested or committed about $6.7 million (Health Canada has spent about $2 million on research, the CIHR has announced or held competitions for $2.7 million and the Minister of Health has reallocated $2 million for SARS research to the NML) on SARS research. This does not account for what has been spent directly by health institutions and provincial governments in responding to SARS. The investment seems small in relation to a problem that infected more than 400 people, killed 44, resulted in thousands in quarantine, shut down the health care system in Toronto, had huge direct and indirect costs, and probably affected national economic indices. It is especially small when one considers that $20 million have been allocated for advertising campaigns to enhance tourism in Ontario post-SARS.

TABLE 3

Canadian Spending On Infectious Diseases Research and SARS Research To Date

	All Infectious Diseases (C$ millions)	Special Allocations for SARS (C$ millions)
CIHR[2]	71.5	2.7
NSERC	2.8	
Genome Canada[3]		
Canada Foundation for Innovation	24	
Networks of Centers of Excellence[4]		
Health Canada – National Microbiology Laboratory (internal and external funding)	13	3
Health Canada – Center for Infectious Disease Prevention and Control (internal and external funding)	5	1
Health Canada – Laboratory for Food Borne Zoonoses (internal and external funding)	5	
Provincial Governments	Unavailable	12
Total	**120+**	**17.7**

In recognition of the unusual nature of SARS and the importance of research, some novel funding initiatives have developed. British Columbia's SARS Accelerated Vaccine Initiative has made $2.6 million available for SARS vaccine development. The Ontario Research and Development Challenge Fund announced $10 million to create an Ontario infectious diseases network. Part of the funding will be to match the support for Ontario-based scientists who are successful in obtaining CIHR funds for SARS research.

All these initiatives are commendable, but the capacity of the research community to respond is limited. The creation of scientific capacity is a long-term process. It involves coordination of support across post-secondary institutions, granting councils, and the health charities, together with an ongoing demand for highly-skilled personnel and a career path that makes a particular field attractive. Furthermore, as the Canadian Veterinary Medical Association [CVMA] highlighted, capacity-building investments must be extended in new directions. Given the importance of zoonoses, the CVMA questions why "virtually nothing" is spent to predict which diseases in animal populations may jump to human communities, and to prevent such cross-species transmission. This capacity-building must involve the private sector as well as the public sector. For example, Canada's Research-based Pharmaceutical Companies suggest that industry is prepared to invest not only in biomedical investigation but broader health research, including social sciences.

In sum, targeted competitions on a short timeline will simply flow more money to already-overloaded investigators or subsidize second-rate research unless a mature scientific community with appropriate breadth and depth exists and is ready to respond to requests for proposals. A careful balance must be struck across three areas of funding: open competitions to support investigator-driven science; targeted competitions that seek to support, preferentially, work in specific areas; and mission-oriented research with a strongly applied focus (as occurs during outbreak investigation).

2 CIHR submission to the National Advisory Committee on SARS and Public Health, July 28, 2003.
3 Genome Canada currently has a competition for applied genomics in health which will invest in infectious diseases.
4 Two networks are funded, the Canadian Bacterial Diseases Network [CBDN] and the Canadian Network for Vaccines and Immunotherapeutics. CBDN funding as a National Centre of Excellence [NCE] is coming to an end. Two NCEs, the Protein Engineering Network of Centres of Excellence [PENCE] and the Mathematics of Information Technology and Complex Systems [MITACS] have funded SARS research projects.

10C.5 Communications

Scientific communication changes substantially in epidemic situations and is fundamentally different from normal processes and procedures. Public communications issues were detailed in Chapter 5. This section considers communication of scientific information within the scientific community, to public health officials, and to the media.

In a non-epidemic situation, research is communicated through peer-reviewed channels—scientific conferences and scientific journals. This process is slow, but valuable because it serves to validate results. Communications with the public happens in most instances after some form of peer review and communication to other scientists. During the SARS epidemic, communications among laboratory scientists nationally and internationally were effective and efficient through the use of international conference calls and the Internet. An important innovation was the impromptu network of laboratories and supporting web page rapidly put in place by WHO. This resulted in a very early exchange of ideas, results, reagents and protocols and significantly speeded up identification of the coronavirus and confirmation of its link to SARS. The framework for international communication and collaboration came together in less than two weeks. This successful process should be studied, codified, strengthened, and replicated wherever necessary.

Nationally, communication of laboratory results was facilitated through dissemination of a summary of laboratory results from the NML. The frequency of production was limited by a weak capacity for analysis at the NML. Other limitations in communication involving laboratories were outlined in Chapter 6. On balance, however, information moved reasonably well.

The same cannot be said for communication about the epidemiologic aspects of the science. Global epidemiology and public health networks did not develop until much later in the epidemic. Nationally, although Health Canada made significant efforts to obtain and communicate information on the epidemiology of SARS, shortcomings in data management and analysis meant that very little in the way of epidemiologic information was generated to communicate. Thus, the issue may be more one of content than communication capacity.

As was true internationally, teleconference calls and the Internet were the basic communication tools used nationally by researchers. Teleconferences were effective but highly inefficient. Individuals who were key players in the response at all levels spent many hours every day on conference calls. From the Health Canada perspective, since the relevant individuals from the most affected areas were stretched so thinly that they were too busy to participate, this led to the Kafkaesque situation where calls involved discussion among regions that were unaffected. Consideration needs to be given to how to improve the efficiency of communication during emergency response, starting with the creation of adequate local and regional activity so that communications can be sustained while the response to an outbreak is underway.

Formal publication of results also changed during SARS. Researchers had the unusual experience of finding that editors of the most respected journals were lobbying for submissions and offering turn around in a matter of days for review and publication of electronic papers. Trends toward rapid e-publication that were already in the offing may have been accelerated by SARS.

During an epidemic, research is conducted in a fishbowl. This meant that during the SARS epidemic, preliminary scientific results were widely reported in the press more or less as the findings were produced. This resulted in considerable pressure on Canadian scientists, and shaped scientific communications in subtle ways. For example, modest and reasoned differences in viewpoints among experts concerning causative agents appeared to be black-and-white disagreements when selected sound-bites were aired or quotes chosen for use by print media. Honest differences should be shared with the public, but the Committee perceives that there was clear scope for better coordination of how scientists communicated with decision makers and the public.

10D. Capacity for Relevant Public Health and Infectious Disease Research in Canada

As one indicator of research spending on infectious diseases, the CIHR now has an annualized commitment of $71.4 million to this broadly-defined field. This investment might be considered "over-invested"[5] if viewed solely with an eye to the relative burden of disease. The problem, of course, is that the CIHR's overall budget on a per capita basis continues to lag hugely behind the US National Institutes of Health. Compared to the USA, spending by our national health research agency on infectious diseases represents a substantial under-investment, and many other areas of health research have presumably fallen even further behind. The CIHR's spending includes 11 randomized controlled trials for a total of $3.88 million, and the HIV Clinical Trials Network for

5 CIHR submission to the National Advisory Committee on SARS and Public Health, July 28, 2003.

$4.2 million; 527 operating grants for $52.6 million; 91 career awards for $5.56 million; and 181 individual training awards for graduate students and post-doctoral fellows for a total of $4.30 million. As an example of under-investment in infectious diseases research, the CIHR currently has no funded projects on West Nile disease.

Epidemiologic and public health research on infectious diseases is considerably under-invested. "CIHR's investment in infectious disease research flows primarily to support biomedical research (84%), and the emphasis on biomedical research in this field is stronger than in the CIHR's overall portfolio (72%)."[6] Furthermore, there are no specific CIHR investments in emerging infectious diseases, although the Institute of Immunology and Infectious Diseases is planning a special initiative in this area. According to a brief inventory by the CIHR, "NSERC provides about $2.8 million in operating support per year in areas ranging from studies into fundamental biology of pathogens, through to more applied studies of vaccines and antimicrobials, agricultural practice, and food safety. As well, "the Canadian Foundation for Innovation has invested close to $24 million in infrastructure and equipment in the area of infection and parasitic diseases." Two federally-funded networks of centres of excellence are relevant: the Canadian Bacterial Diseases Network and the Canadian Network of Vaccines and Immunotherapeutics [CANVAC]. There is no network focused on viral diseases. "Genome Canada has funded three large projects relevant to human infectious disease, on Cryptococcus, *Candida albicans*, and viral proteomics."

Other relevant federal investments include the National Research Council's Institute of Biodiagnostics located in Winnipeg and its Institute of Biological Sciences, located in Ottawa. The latter has developed an effective vaccine for Group C meningococcal disease.

According to the CIHR, "A ballpark estimate for federal investment in infectious diseases research would be $100 million per year. However, as in most other areas of science, there is little coordination between agencies in how those funds are invested or in developing a federal research agenda."

We have noted above that essential capacity for leading and performing the needed research in response to an epidemic must reside in government-funded public health institutions. How robust is the capacity for this type of research in public health institutions? The Committee perceives that, with a few exceptions, the overall research capacity in provincial public health is limited. Ontario has seen a decline in the number of laboratory scientists in its provincial laboratory; analytical capacity in the provincial public health branch was notably limited during SARS. British Columbia, Alberta and Quebec have strength in some areas, but no other provinces have internationally-competitive laboratory research capacity in the public health realm.

The situation is worse in the epidemiologic and public health fields. The Committee's assessment is that, with the possible exception of Quebec's National Institute of Public Health, no province has broad public health research capacity within its public sector. British Columbia has strength in specific areas through its Centre for Disease Control. Manitoba at one time had a productive epidemiologic research unit but it has largely disintegrated owing to lack of targeted support. We detailed earlier the loss of Ontario's PHRED program and the lack of linkages between health units and universities or community colleges. The same malaise that has led to profound shortages in human resources for public health has undermined research capacity in the field.

Recognizing the capacity issues, the CIHR has recently funded five new strategic training initiatives in infectious diseases. This is a positive step, but CIHR's record shows that its absolute increases in support for biomedical science have meaningfully outstripped expansion across the other three "pillars" combined—those being clinical investigation, health services research, and population and public health research. This asymmetric growth in CIHR spending is partly a capacity problem in areas other than biomedical research, but also reflects the CIHR's difficult mandate of meeting research needs for all imaginable stakeholders. It is very unclear whether the separate CIHR Institutes can address the capacity for public health research, particularly in epidemiology and the social and behavioural sciences.

10E. Recommendations

Some aspects of the research response to SARS went exceedingly well in Canada; other aspects did not. The reasons for these failings can be summarized briefly as follows. Governments have not consistently recognized that research is a core public health function, and supported it. Canada's considerable new investment in research has not adequately targeted public health and epidemiologic research, nor has there been substantial thinking about creative partnerships and programs to

6 CIHR submission to the National Advisory Committee on SARS and Public Health, July 28, 2003.

build public health research capacity. Furthermore, support for clinician scientists has been limited. Canadian research structures and procedures are not designed for the type of research response that is required in an epidemic. The actual capacity for key types of research in public health institutions has been constrained by: the weak research and evaluation culture in multiple levels of governments; limited career paths for public health practitioners in various disciplines at the federal, provincial, and local levels; a lack of programs and opportunities to prepare personnel from multiple disciplines for public health research in general and investigation of emerging infectious diseases in particular; and pressure on existing personnel such that research and evaluation activities, if funded at all, must be squeezed in between other pressing work demands. Finally, there are no mechanisms for national leadership, coordination and direction of epidemic research.

To prepare for future SARS outbreaks, which could be as close as the next respiratory virus season, Canada needs to take stock and complete some important SARS-related research projects as quickly as possible. We also need to make longer-term changes. Although SARS was only a moderate-sized outbreak, it highlighted a number of deficiencies in our research response that could have been extraordinarily damaging had the agent been even more infectious or dangerous. We now have the opportunity—indeed, an obligation—to address the structural, procedural and capacity issues that prevented a more effective research response to SARS in this nation.

The Committee accordingly recommends that:

10.1 The Canadian Agency for Public Health should earmark substantial funding to augment national capacity for research into epidemiologic and laboratory aspects of emerging infectious diseases and other threats to population health. This enhanced national public health science capacity should be strongly linked to academic health institutions through co-location, joint venture research institutes, cross appointments, joint recruitment, interchange, networks and collaborative research activities.

To this end, in the notional core budget for the Canadian Agency for Public Health outlined in Chapter 3, we foresaw new spending rising to $50 million per annum on infectious disease capacity, including research elements, and another $25 million in general public health R&D functions. Some of these activities would be in-house; many would be initiated in collaboration with academic partners, provinces and territories, major municipal health units, and research agencies, particularly the CIHR.

10.2 The Canadian Agency for Public Health, in partnership with provincial and territorial governments and through the F/P/T Network for Communicable Disease Control, should directly invest in provincial, territorial, and regional public health science capacity.

The $100 million earmarked for 'second-line' capacity, including the operation of the F/P/T Network for Communicable Disease Control, is the logical source of funding for this purpose. Options include directed funding flows to existing provincial/territorial bodies or the creation of joint F/P/T regional institutes. The mandate of these bodies would be to provide public health research services to the provinces and territories.

10.3 The F/P/T Network for Communicable Disease Control, in partnership with the CIHR and the Canadian research community, should develop clear protocols for leadership and coordination of future epidemic research responses.

10.4 The Canadian Agency for Public Health and the F/P/T Network for Communicable Disease Control should ensure that epidemic response teams initiated as part of the Health Emergency Response Team [HERT] concept, provide not only surge capacity for outbreak containment per se, but also a mobile "B-team" and investigative infrastructure, including epidemiologists, programmers, and analysts.

10.5 The Canadian Agency for Public Health, in partnership with provincial/territorial governments, should develop clear rules, reinforced by intergovernmental agreements, on the sharing of information, the establishment of national databases, and the use of biologic materials for research in response to epidemics.

10.6 The Canadian Agency for Public Health, in collaboration with the CIHR, should establish a task force on emerging infectious diseases to recommend research priorities and funding mechanisms. The Agency, in collaboration with the CIHR and other national research funding bodies, should support the development of special funding mechanisms and processes for fast-tracking research related to epidemics of infectious diseases.

10.7 The Canadian Agency for Public Health, in partnership with research agencies and provincial/territorial governments, should work with universities to improve research training opportunities in infectious diseases and outbreak management for the full range of involved disciplines. This capacity-building focus should be a priority within the broader health human resource strategy of the Agency (see Chapter 7).

10.8 The Government of Canada should strengthen its R&D functions in international health outreach, with particular emphasis on emerging infectious diseases on a global basis.

In this respect, as suggested in the brief discussion of ethics in Chapter 9, the Committee believes that Canada has an obligation to be more engaged in outreach activities that will help build research capacity in less developed nations. These investments should have positive long-term impacts on the health of populations in those nations, and thereby complement conventional forms of assistance provided by the Canadian International Development Agency and other agencies. We return to this issue in Chapter 11.

10.9 The Government of Canada should foster workable public-private partnerships with the biotechnology, information technology, and pharmaceutical industries for shared research interests in the realm of emerging infectious diseases, including new vaccines, antiviral compounds, immunotherapies, and diagnostic technology.

10.10 The Canadian Agency for Public Health should spearhead discussions on the issues of intellectual property, copyright and patenting from public health inventions.