Lessons from SARS

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Although efforts to contain the spread of severe acute respiratory syndrome have succeeded remarkably well in some countries it seems unlikely that SARS will be deleted from the planet any time soon. In China the number of new cases rises unabated and threatens to overwhelm local public health capacity. Global eradication may have to await the development of a vaccine.

And yet, as we go to press, the situation in Canada seems more hopeful than it has for some time. The apparent containment of the outbreaks in Toronto and Vancouver can be attributed to astute clinicians who recognized the unusual features of the first cases and were alert to early warnings of an emerging atypical pneumonia in the Far East.[1] We should also be thankful for the hard work of public health officials who, notwithstanding concerns about public health preparedness that have been raised in recent times (including in this column),[2] have done a superb job.

Nonetheless, the blame game has begun: provincial ministers criticize their federal counterparts, and federal politicians snipe at one another. Ontario's premier has explained that he viewed SARS as a matter for medical experts, not politicians. Certainly, one would not want the response to a public health crisis to become distorted by political agendas. But it is still important to ask whether we have the right structures in place to enable adequate leadership, both medical and political, at such a time. We need to ensure we have the capacity to detect and manage emerging infectious diseases. We need to take seriously the epidemiologic implications of international air travel, the globalization and industrialization of our food supply, and climate change.

Historically, the spread of contagious disease followed the routes of commerce and exploration. Now, imported infectious agents may be as close as the local supermarket, or among the next arrivals at any international airport. During the year 2000 almost 100 million nonresident passengers arrived in China, Hong Kong and Vietnam, and almost 500 000 residents of these countries travelled to the United States.[3] Less than 6 weeks after the first SARS cases were officially reported in Guangdong Province, China, the world map was dotted with SARS outbreaks in 27 countries.

The initial cases of SARS appeared in Guangdong Province no later than Nov. 16, 2002. The World Health Organization was notified by the Chinese Ministry of Health 3 months later, on Feb. 11, of an outbreak affecting 305 individuals, with 5 deaths.[3] It was not until Mar. 12, when the disease had reached Hong Kong, that WHO issued a global alert. As new infectious threats emerge we will need a better early detection and warning system, one that will also work in overcrowded (and usually poor) regions with limited resources. We have arms detectors; perhaps we need an equally determined corps of disease detectors.

The first case of SARS in Canada was diagnosed on Mar. 13, the day after WHO issued the global alert.[4] Yet, 2 weeks later, some patients with SARS were not being managed in isolation, perhaps contributing to the widespread outbreak in Toronto, particularly among health care professionals.[5,6] Is our surveillance and reporting system adequate? Are front-line clinicians getting the information they need, when they need it? Do local and provincial public health officials have the training and resources they need to carry out effective surveillance and disease control? Even in the pre-SARS era, there was considerable evidence that they don't.[2]

And, finally, there is the vexing problem in Canada of public health leadership and jurisdiction. Is federal–provincial public health collaboration adequate? Should Health Canada be leading, or coaching? Many politicians are discovering what an epidemic curve looks like and why it is important. They have attempted to respond to an epidemic of fear by dining out conspicuously in Toronto's Chinatown and by releasing short-term financial assistance to affected individuals and hospitals. What we need now is a hard look at public health responsiveness in the long term. The next "SARS" could easily be more contagious and more virulent. We were lucky that the initial outbreak of SARS was in Toronto, a city with excellent and abundant clinical and public health resources. But this is not true everywhere in Canada.[2] We need to question (again) the wisdom of embedding our national public health system of disease control and prevention in a large government bureaucracy. Our governments should look beyond today's epidemic curves and prepare for the next. A good first step would be the creation of a Canadian Office of Disease Control and Prevention. — *CMAJ*

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Leçons tirées du SRAS

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Même si les efforts déployés pour enrayer la propagation du syndrome respiratoire aigu sévère (SRAS) ont connu un succès remarquable dans certains pays, il semble peu probable que l'on réussira à éradiquer bientôt le SRAS de la planète. En Chine, le nombre de nouveaux cas continue de grimper et menace de déborder la capacité des services de santé publique locaux. L'éradication mondiale devra peut-être attendre la mise au point d'un vaccin.

Pourtant, au moment d'aller sous presse, la situation au Canada semble devenue plus encourageante. Les éclosions à Toronto et Vancouver semblent confinées, grâce à des cliniciens astucieux qui ont reconnu les caractéristiques inusitées des premiers cas et sont demeurés à l'affût des premiers signes de l'émergence en Extrême-Orient d'une nouvelle pneumonie atypique[1]. Il faut aussi remercier les dirigeants de la santé publique qui, par leurs efforts inlassables, ont fait un travail superbe en dépit des préoccupations soulevées récemment (y compris dans cette chronique) au sujet de l'état de préparation du système de santé publique[2].

La guerre des reproches est néanmoins déclenchée : les ministres provinciaux critiquent leurs homologues fédéraux et les politiciens fédéraux se canardent mutuellement. Le premier ministre de l'Ontario a expliqué qu'il considérait que le SRAS relève de la compétence des experts de la médecine et non de celle des politiciens. Personne ne voudrait certes que des programmes politiques déforment la réponse à une crise en santé publique. Il importe quand même toutefois de nous demander si nous avons les bonnes structures pour assurer un leadership adéquat, tant médical que politique, dans une telle crise. Nous devons nous assurer d'avoir la capacité de repérer les maladies infectieuses émergentes et de les prendre en charge. Il faut prendre au sérieux les répercussions épidémiologiques des voyages aériens internationaux, de la mondialisation et de l'industrialisation de l'approvisionnement en aliments, ainsi que des changements climatiques.

Dans l'histoire, les maladies contagieuses se sont toujours propagées en suivant les voies du commerce et de l'exploration. Des agents infectieux importés peuvent maintenant se retrouver aussi près qu'au supermarché local ou chez les prochains arrivants à n'importe quel aéroport international. En 2000, presque 100 millions de passagers non résidents sont débarqués en Chine, à Hong Kong et au Vietnam et presque 500 000 résidents de ces pays se sont rendus aux États-Unis[3]. Moins de six semaines après le signalement officiel des premiers cas de SRAS dans la province du Guangdong, en Chine, la carte du monde était pointillée d'éclosions de SRAS dans 27 pays.

Les premiers cas de SRAS étaient apparus au Guangdong dès le 16 novembre 2002. Le ministère chinois de la Santé a prévenu l'Organisation mondiale de la santé trois mois plus tard, soit le 11 février, d'une éclosion ayant infecté 305 personnes et causé cinq décès[3]. L'OMS a lancé un avertissement mondial le 12 mars seulement, lorsque la maladie a atteint Hong Kong. À mesure que de nouvelles menaces infectieuses feront leur apparition, nous aurons besoin d'un meilleur système de détection précoce et de préalerte qui fonctionnera aussi dans des régions surpeuplées (et habituellement pauvres) disposant de ressources limitées. Nous avons des détecteurs d'armes : nous avons peut-être besoin aussi d'un groupe tout aussi déterminé de détecteurs de maladies.

Le premier cas de SRAS au Canada a été diagnostiqué le 13 mars, le lendemain de la diffusion de l'avertissement mondial de l'OMS[4]. Or, deux semaines plus tard, certains patients atteints du SRAS n'étaient pas encore traités en isolation, ce qui a peut-être contribué à l'éclosion généralisée à Toronto, surtout chez les professionnels de la santé[5,6]. Notre système de surveillance et de notification est-il adéquat? Les cliniciens des premières lignes obtiennent-ils les renseignements dont ils ont besoin au moment où ils en ont besoin? Les dirigeants locaux et provinciaux de la santé publique ont-ils la formation et les ressources nécessaires pour assurer une surveillance efficace et contrôler la maladie? Même avant le SRAS, les preuves démontraient amplement que non[2].

Il y a enfin le problème vexant au Canada du leadership et des compétences en santé publique. La collaboration fédérale–provinciale en matière de santé publique est-elle adéquate? Santé Canada devrait-il diriger ou encadrer? Beaucoup de politiciens découvrent à quoi ressemble une courbe épidémique et la raison de son importance. Ils ont essayé de réagir à une épidémie de peur en sortant officiellement dans les restaurants du quartier chinois de Toronto et en accordant de l'aide financière de courte durée aux personnes et aux hôpitaux touchés. Ce qu'il nous faut maintenant, c'est analyser de près la capacité à long terme de réaction du secteur de la santé publique. Le prochain «SRAS» pourrait facilement être plus contagieux et plus virulent. Nous avons été chanceux que l'éclosion initiale de SRAS se produise à Toronto, qui dispose de ressources cliniques et de santé publique excellentes et abondantes. Ce n'est pas le cas partout au Canada[2]. Nous devons nous interroger (encore) sur la sagesse d'intégrer dans une énorme bureaucratie gouvernementale notre système national public de contrôle et de prévention des maladies. Nos gouvernements devraient voir plus loin que les courbes épidémiques d'aujourd'hui et se préparer à la prochaine éclosion. La création d'un Bureau canadien du contrôle et de la prévention des maladies constituerait un bon premier pas dans cette voie. — *JAMC*

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Dr. John Brackenbury/Science Photo Library

West Nile virus

West Nile virus (WNV) has been described in Africa and the Middle East since the 1930s, but it was only when the illness surfaced in New York City in 1999 that it started to command attention in North America. Since then the disease has spread, and in 2002 the WNV outbreak in North America was the largest ever documented. Caitlin Pepperell and colleagues describe the clinical characteristics of 64 patients admitted to hospital in southern Ontario and retrospectively identified as having been infected with WNV. They describe patient demographics, clinical presentation, neurological manifestions and course in hospital. Of greatest concern is the finding that most of these patients were previously active and living independently in the community, but suffered severe morbidity and mortality. Bob Nosal and Rosana Pellizzari offer a primer on WNV in our Public Health pages. In a related commentary, Howard Shapiro and Sandra Micucci describe how a full response to WNV consists of public education, surveillance and mosquito control; particular attention is paid to the effectiveness and safety of pesticides.

See pages 1399, 1427, 1443 and 1455

Differences in operative mortality

In Canada, regionalization of health services has caused considerable controversy. Advocates for regionalization of surgical procedures, particularly complex ones, often maintain that outcomes are better at hospitals where these operations are performed more frequently. David Urbach and colleagues tested this hypothesis by collecting data concerning 31 632 people who underwent 1 of 5 surgical procedures (2 with high and 3 with low operative mortality) and compared the results from Ontario hospitals with higher and lower operative frequency. They found that restricting some complex procedures to high-volume hospitals might prevent a small number of deaths.

See page 1409

SARS

When severe acute respiratory syndrome (SARS) hit Canada, it hit quickly. Several hospitals in Toronto found themselves dealing with an extremely contagious disease whose cause, diagnosis and treatment were unknown. The earliest cases presented to community hospitals and, before a diagnosis could be made, infection was passed both to fellow patients and to hospital staff. Hy Dwosh and coworkers describe the pattern of transmission at their community hospital in Richmond Hill, Ont., precipitated by a patient requiring urgent hemodialysis who had been transferred to their hospital after being exposed to SARS at another institution. They describe the clinical course of the subsequent cases and the ensuing public health response, which involved the quarantine of over 5000 people, and trace the pattern of infection that resulted in 15 suspected or probable cases of SARS.

In a related commentary, Richard Schabas argues that the perceived risk of SARS in Canada is disproportionate to the actual risk of getting the disease. He cautions that the actions of the public and their health officials should be based on facts and experience, not fear. In a second commentary, Guénaël Rodier, Director of the World Health Organization's Communicable Disease Surveillance and Response division, explains why Toronto was targeted for a worldwide travel advisory, and why this decision was reversed shortly after its announcement.

Canapress

See pages 1415, 1432 and 1434

Physicians for oral health

On behalf of the dentists of Ontario, I wish to commend you for emphasizing to Canadian physicians, through your public health column, the issue of dental caries.[1] It is reassuring to the dental profession when physicians are reminded of the importance of oral health as a major component of general health.

I suspect that the groups that Erica Weir identified as carrying the "burden of oral disease"[1] also bear a significant burden of systemic disease. Physicians probably see patients at risk for dental disease more frequently than dentists, and this opportunity to establish basic awareness of the need to prevent dental caries and periodontitis should not be missed.

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Pertussis control in Canada

The outbreak of pertussis in a refinery as described by John Hoey in a recent article on pertussis in adults[1] is interesting but pales in comparison with outbreaks recently reported from Vancouver Island, where well over 100 positive cases (by both culture and polymerase chain reaction) were diagnosed in adolescents and adults,[2] and from Quebec, where the severity of pertussis in older adults was well characterized.[3] Rarely, pertussis can lead to severe complications, even in a healthy adult.[4]

The case-fatality rate of 0.8% reported by Hoey actually represents cases in infants under 2 years of age admitted to hospital.[5] The overall case fatality rate is unknown but is undoubtedly lower.

There are a number of differences between the United States and Canada in recommendations for treatment and chemoprophylaxis of pertussis contacts. In Canada, treatment and chemoprophylaxis with erythromycin are recommended for 10 days rather than 14, and the maximum daily dose is 1 g rather than 2 g.[6] Also, chemoprophylaxis is recommended in this country only in households or other environments where there is an infant under 1 year of age. Canadian guidelines will soon be revised according to the recommendations of the National Consensus Conference on Pertussis (held in May 2002). On the basis of results from 4 randomized controlled trials, the recommended treatment for pertussis will be 7 days of erythromycin,[7] 5 days of azithromycin[8] or 7 days of clarithromycin,[9] and chemoprophylaxis will be limited to households with an infant under 1 year of age (because of lack of benefit in modifying the development of clinical disease in contacts[10]).

The recommendations for vaccination presented by Hoey were those of the US Centers for Disease Control and Prevention. In Canada, an adolescent/adult formulation of acellular pertussis vaccine combined with diphtheria and tetanus toxoids (known by the abbreviation TdaP; Adacel, Aventis Pasteur) is licensed for use in people 12 to 50 years of age. The National Advisory Committee on Immunization recommends that all adolescents receive TdaP in place of Td.[11] More extensive use of this vaccine beyond adolescence may be beneficial in controlling the increasing burden of disease in adults.

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Safe use of acetaminophen

A safety update on acetaminophen[1] published in the Oct. 29, 2002, issue of *CMAJ* mentioned that "[t]he number of cases of hepatotoxicity that occur in Canada each year is not known, and Health Canada is not currently reviewing the packaging and warning labels for the drug in this country."

Health Canada issued a public advisory about acetaminophen[2] on Feb. 13, 2003. This advisory emphasizes that products with different names may contain the same active ingredients and that it is important to read the labels of all medications carefully to avoid unintentional overdose. Health Canada has also published a more general article on the safe use of medicines in the "It's Your Health" series.[3] Both articles are available online, for the benefit of physicians and their patients.

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Enlightening medical students

The recent report by Johane Patenaude and associates[1] about the levelling of moral reasoning among medical students during their years in medical school does not surprise me. The environment to which students are exposed in teaching hospitals might be one aspect of their training that inhibits the development of moral reasoning.

I work in the inpatient psychiatry unit of a teaching hospital. Every few months, all staff psychiatrists receive a compilation of length-of-stay statistics, "savable days" and other related data, listed by individual staff member. I believe that this practice is common in other departments and hospitals as well. Through this process, staff are openly ranked according to the speed with which they discharge their patients, the worst offenders (those who keep their patients in hospital the longest) appearing at the top of the list. These reports, masquerading as "information," represent an example of public shaming, a descendent of tarring and feathering, head shaving and public hanging. This practice encourages staff to regress in their moral development to Kohlberg's stage 3,[2,3] interpersonal conformity, the stage to which the students in Patenaude and associates' study tended to move (from lower or higher stages).

I wait in vain for rankings of humanistic parameters such as compassion, empathy and supportiveness toward patients, or even simpler measures such as providing good treatment or treating other staff well.

Is it any surprise that our students do not progress to higher moral levels?

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In their study on students' moral development, Johane Patenaude and associates[1] appropriately focus attention on an often-overlooked area of undergraduate medical education. Yet it seems a shame to spend time and money on yet another study confirming the deficiencies of undergraduate medical education. Instead, we should begin the more difficult task of making and assessing needed changes in the curriculum. As Peter Singer points out,[2] we know what needs to be done, but as yet "none of these strategies has been taken very far." Why the lack of progress?

Perhaps it has something to do with the reality that teaching remains undervalued. Yes, we need to create an "ethical learning climate" for our students, and we can begin by creating an ethical teaching environment for our teachers.

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Transmission of HPV

John W. Sellors and colleagues[1] have described human papillomavirus (HPV) infection in women, relating this infection to various risk factors, including number of previous sexual partners. It should be pointed out, however, that HPV is not a typical sexually transmitted infection.

As the recent paper by Winer and associates[2] highlighted, sexual contact is not necessary for the transmission of HPV. Although these authors showed that the cumulative incidence of HPV over the first 4 years after first sexual intercourse was about 50%, they also showed that HPV infection was acquired by virginal women at a cumulative rate of 7.9% over 2 years. According to these authors, abstaining from penetrative sex did not protect women from HPV transmission, and they proposed that skin-to-skin contact during nonpenetrative sexual contact may be a primary mode of genital HPV transmission.

Furthermore, no protective effect has been associated with condom use.[3] This failure to prevent HPV may be related to the poor validity of self-reported condom use, condom breakage, slippage and incorrect use, but it may also be caused by the ability of biological material to pass through condoms.[4]

Perhaps researchers should move away from collecting data on the number of previous sexual partners a woman has had, especially given that data of this type help to stigmatize HPV as a virus affecting only promiscuous women who have unprotected penetrative sex.

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[Four of the authors respond:]

As Sarah Giles points out, nonpenetrative sexual activity is associated with increased risk of genital HPV infection.[1] We did not define sexual activity when we asked women to report the number of their sexual partners.[2] However, it is likely that at least some respondents included partners with whom sexual activity was nonpenetrative.[3]

We also agree with Giles that evidence for the protective effect of condoms against HPV infection is lacking.[4]

Giles raises an important issue regarding the potential stigmatization of women with genital HPV infection. Approximately 65% of women (or more) have been infected with HPV sometime in their lives, the vast majority of these infections being transient.[5] It is reasonable to assume that the same proportion of men are infected, given that the risk factors for genital HPV infection are similar in men and women.[6] Such infection is therefore widespread and common, especially at younger ages. To assume that any particular infected individual has had numerous sexual partners is wrong. Although an increasing number of partners does increase the risk of infection, sole contact with one infected partner can lead to acquisition of genital HPV.[7]

Nevertheless, as research has shown, a certain proportion of women and men with HPV infection have had numerous sexual partners.[2,6,7] A MEDLINE search for the period January 1966 to March 2003, using "human papillomavirus" as a subject heading and "promiscuity" as a keyword, identified 7 articles that used the word "promiscuous" in the abstract when referring to such a sexual history in people infected with genital HPV. We believe that terms such as this one are morally charged and judgement laden, and that they should be avoided by physicians and researchers.

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ECT for Parkinson's?

Mark Guttman and associates,[1] in their review of diagnosis and management of Parkinson's disease, make no reference to electroconvulsive therapy (ECT) as an option for patients with insufficient response to pharmacotherapy.

The most contemporary and authoritative review of psychiatric practice in this field[2] strongly endorses the use of ECT for the management of refractory Parkinson's disease, citing numerous references from the neurology and psychiatry literature in support of this endorsement. Many psychiatrists who administer ECT are aware of this literature.

I would appreciate the authors' comments on the available evidence for the effectiveness of ECT in Parkinson's disease. If warranted, ECT should then be given its appropriate place in the treatment algorithm for this illness.

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[One of the authors responds:]

Although we did not mention ECT in our article,[1] we agree that it may have a role in the treatment of specific symptoms of Parkinson's disease.

Parkinsonian patients who are severely depressed and whose condition is refractory to antidepressant therapy are candidates for ECT to treat their depression. Patients with drug-induced psychosis that is resistant to atypical neuroleptic medication who cannot tolerate reductions in their antiparkinsonian medication may also be candidates for ECT. However, ECT should not be offered to patients with dementia because there is the potential that such treatment may cause worsening of cognition and may induce delirium. There is insufficient evidence to suggest that motor symptoms related to Parkinson's disease should be treated with ECT, and in our opinion this should not be considered an indication for its use.

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The return of "negative" trials?

I was surprised that several important issues were not addressed in the original reports[1,2] and editorial[3] about rate versus rhythm control in atrial fibrillation published in the *New England Journal of Medicine*, or in the review[4] and editorial[5] published subsequently in *CMAJ*.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators found no statistically significant difference between rhythm control and rate control.[1] However, one cannot rule out the possibility of a type II error, given that a sample size of 5300 was planned[6] but only 4060 patients were enrolled in the study.

In the noninferiority study by Van Gelder and associates,[2] the efficacy of rate control was within the upper bound of the 95% confidence interval of that of rhythm control. However, 3 concerns must be addressed.

First, it is not clear if the rhythm control strategy is a suitable active comparator. Neither the authors nor the practice guidelines cited[7] provided details on any earlier trials that showed rhythm control to be consistently better than placebo. Thus, it is not possible to assess the similarity of the current trial to those earlier trials, the expected effect size of rhythm control relative to placebo[8] or the consistent responsiveness to rhythm control of the composite endpoint components[9] used in the current trial.

Second, the investigators performed an intention-to-treat analysis only, which gives a conservative estimate of the effect size and hence bias toward a conclusion of noninferiority, when a per-protocol analysis is generally preferred.[10]

Finally, neither the AFFIRM trial[1] nor the noninferiority study[2] defined or reported compliance. Poor compliance can create bias toward a conclusion of "no difference" in both cases and would be of particular interest in assessing life-long therapies with recognized adverse effects.

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Competing interests: None declared.

[Dr. Nattel responds:]

Mario de Lemos raises several points concerning the trials of atrial fibrillation management that I discussed in my commentary.[1]

First, he asks whether a type II error might have occurred in the AFFIRM trial,[2] given the difference between the planned sample size and study enrolment.[3] The selection of appropriate sample size always involves estimating a clinically relevant difference and calculating the sample size needed to detect this difference with acceptable power. The sample size was reduced to 4060 to ensure sufficient power to reliably detect a difference of 30%, which was felt to be a minimally important clinical difference.[4] The mortality rate in AFFIRM was marginally higher (by 15%, $p = 0.08$) in the rhythm-control group. The primary finding of AFFIRM was that a rate-control approach is not inferior to a rhythm-control approach. A larger sample size (and 5300 patients might not have been sufficiently large) might have detected a statistically significant increase in mortality rate with rhythm control; however, the investigators judged that the differential impact of a significant p value for this small effect was not sufficient to justify the substantial additional cost (and the potential detrimental effect of exposing additional patients to nonsuperior and more complex rhythm-control therapy) of extending the trial.

De Lemos also states that the efficacy of rate control was within the upper bound of the 95% confidence limit of that of rhythm control in the trial by Van Gelder and associates.[5] However, those authors did not use efficacy as an endpoint. Their primary endpoint was a composite index of cardiovascular death, heart failure, thromboembolic complications, bleeding, pacemaker implantation and severe adverse drug reactions. In fact, the primary endpoint (which was a negative outcome) was more prevalent in the rhythm-control group, with the 90% 2-sided confidence limit barely including a neutral effect.

De Lemos further argues that it is unclear whether the rhythm-control strategy was a suitable active comparator. This statement seems to miss the point of the trials, which was to compare the 2 widely used approaches to therapy for atrial fibrillation: rate versus rhythm control. Both studies used patient populations in which recurrence was deemed likely, so a placebo group might not have been ethical in light of presently accepted medical practice.

De Lemos also criticizes use of an intention-to-treat analysis, rather than a per-protocol analysis (in which only events while the patient is receiving active therapy are analyzed), which he claims "is generally preferred." In fact, the weight of clinical trials opinion favours intention-to-treat analyses. The simplest way to understand the advantage of an intention-to-treat approach is to imagine a therapy that has a neutral effect on outcome but a high frequency of side effects in high-risk patients. Such a drug would be discontinued in many high-risk patients. With a per-protocol analysis, there would be an appearance of a better outcome among patients maintaining therapy, but this would be due to the drop-out of high-risk patients rather than a direct benefit.

Finally, de Lemos criticizes the AFFIRM[2] and Van Gelder and associates[5] trials for not defining compliance. Because both trials assessed approaches to therapy (rate versus rhythm control), compliance would have been difficult to define. It would presumably include such standard measures as taking prescribed medication, but also reporting of events, acceptance of cardioversion when prescribed, and even physician-based components such as vigour of pursuit of heart-rate and sinus-rhythm endpoints.

It must be kept in mind that the goal of these studies was to compare 2 widely used strategies in a clinically relevant context, a goal that was largely

achieved. It is true that as physicians we prefer "positive" trials because they leave us with a sense of a conclusive message. However, both the AFFIRM[2] and Van Gelder and associates[5] trials did yield a conclusive and important message, that for presently available approaches to atrial fibrillation therapy, rate control is not inferior overall to rhythm control. It is debatable whether larger studies that achieved a statistically significant *p* value would have provided any more practical information.

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Competing interests: None declared.

First-use risks

Eric Wooltorton[1] has written a balanced article in response to the warning on Diane-35 and the risk of venous thromboembolism issued by Health Canada.

Caution is always required in prescribing estrogen–progestin combinations, whether for contraception, postmenopausal hormone replacement or treatment of acne. However, the risk attributed to preparations containing cyproterone acetate in comparison with other preparations may have been exaggerated by not taking first-time use into account. This effect has been estimated[2] to increase the risk of venous thromboembolism 10-fold in the first year of oral contraceptive use, regardless of preparation. The research letter of Vasilakis-Scaramozza and Jick,[3] which was used by Health Canada to support the increased risk, provided adjusted odds ratios for venous thromboembolism, but no reference is made to first-time use as a potential factor. That report described a total of 128 subjects (cases and controls) who had used levonorgestrel-containing preparations and 42 subjects (cases and controls) who had used preparations containing cyproterone acetate. In the first group, only 9 (7%) had used the preparation for 6 months or less, whereas in the second group, a much larger proportion (12 or 29%) had used the drug for 6 months or less. Among patients with this short duration of use, there is a greater probability of first-time use. Thus, the proportion of women using an estrogen–progestin combination for the first time appears to have been higher in the group receiving preparations containing cyproterone acetate, which might account for some or all of the greater risk of venous thromboembolism in that group.

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Competing interests: Dr. Rowe has received speaker fees from Wyeth, Organon, and Berlex Canada.

QALYs: the best option so far

I would like to challenge Maurice McGregor's argument in a recent commentary[1] that because the quality-adjusted life-year (QALY) has "severe limitations," it is not useful for cost-utility analyses.

To support his argument that the QALY is not meaningful, McGregor quotes a seminal work emphasizing the difficulty of using a single measurement to evaluate different health outcomes.[2] However, this same text recommends the continued use of the QALY while researchers develop potentially better tools.[2]

McGregor also argues that the QALY is not valid because it "frequently violates societal concerns for fairness in the allocation of health care resources." Such ethical concerns have been expressed before, but alternatives to circumvent them are still relatively nascent, and "the conventional QALY remains the dominant approach."[2]

McGregor then contends that the QALY is not reliable because utility estimates vary with the method used. However, variability can occur in any research. Consider how frequently clinical studies yield conflicting results. A more pertinent question is whether this variability is truly fatal to interpreting cost-effectiveness analyses.

McGregor next argues that the QALY is not relevant because there is "no unanimity as to whose viewpoint should be used when making societal policy decisions." This does not make the QALY irrelevant — it merely means that research is needed to clarify the issue.

McGregor's final argument is more a general cautionary statement: "When the studies with which the cost–utility analysis in question can be compared are not identified, the cost–utility analysis should clearly not be used in health policy decisions." However, the same can be said in any field: comparators should always be identified. Furthermore, comparing one cost-effectiveness ratio with another is no different from using league tables based on number-needed-to-treat to evaluate the clinical effectiveness of interventions.[3]

Without doubt, the QALY is an imperfect outcome measure. Nonetheless, despite acknowledging its weaknesses,

the 1996 Panel on Cost-effectiveness in Health and Medicine endorsed its use.[4] Reporting "outcomes in natural units," as McGregor suggests, detracts from the goal of developing an ideal measure incorporating both quantity and quality of life.

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[The author responds:]

I regret that I cannot accept Christopher Chong's "challenge," which is based on a misinterpretation of my commentary.[1] Nowhere did I argue that "because the quality-adjusted life-year (QALY) has 'severe limitations' it is not useful for cost-utility analyses." Of course it is useful. My argument is rather that those severe limitations must be well understood by any decision-makers who would use the QALY in making health policy decisions.

There is no dispute that estimates of utility vary according to how and from what viewpoint they are made. My point is that if such estimates are to be used in health policy decisions, this variability must be understood by the decision-makers. Most decision-makers would probably be astonished to learn that utility is not a constant unit of measurement and that it can only validly be used to compare one health option with another when the health preferences have been estimated by the same method and from the same viewpoint.

As for there being no difference between comparing cost-effectiveness ratios and "using league tables based on number-needed-to-treat to evaluate the clinical effectiveness of interventions," the issue is again the extent to which the decision-makers understand the units of measurement they are employing. I suspect that clinicians understand the index number-needed-to-treat far better than health care administrators understand utilities and QALYs.

And of course I agree that we should continue to try to develop "an ideal measure incorporating both quantity and quality of life." But if the imperfect measurements that we have developed up to this time are used in health policy decisions, the imperfections must be acknowledged and understood by the users.

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Why choose ophthalmology?

In a "Pulse" article earlier this year,[1] Patrick Sullivan hypothesized that "Because the number of call hours can seriously hamper family and other activities, it is probably no coincidence that specialties with less onerous call schedules, such as dermatology and ophthalmology, tend to be oversubscribed in annual residency matches." However, he presented no statistical information to justify this theory.

In the CMA's annual Physician Resource Questionnaire for 2002,[2] only 40 ophthalmologists were surveyed. Of these, approximately 20% had more than 180 hours of call per month;[2] this is only slightly less than the 25% of surgical specialists with this level of call reported by Sullivan.[1]

According to statistics from the Canadian Resident Matching Service, the ratio of the number of applicants whose first choice of specialty was ophthalmology to the number of spaces available was approximately 2:1 for 1998 to 2002.[3] Cardiac surgery, diagnostic radiology, emergency medicine, plastic surgery and dermatology had similar ratios over the same period. Yet the on-call duties of the first 4 specialties in this list are also onerous, at least from what we have observed in our centres. The "oversubscription" Sullivan describes is therefore more likely a result of the number of residency positions in the smaller specialties being too low in relation to societal needs.

We suspect that the popularity of ophthalmology is determined by a variety of factors, such as interest in the specialty, advances in treatment, and perceived benefit to patients and society, rather than on-call duties.

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Correction

Dr. Douglas Cram[1] of London, Ont., was predeceased by his wife, Madeline. Because of an editing error, incorrect information appeared in a recent death notice.

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West Nile virus infection in 2002: morbidity and mortality among patients admitted to hospital in southcentral Ontario

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ß See related articles pages 1427, 1443 and 1455

Abstract

Background: In August and September 2002 an outbreak of West Nile virus (WNV) infection occurred in southern Ontario. We encountered a number of seriously ill patients at our hospitals. In this article we document the clinical characteristics of these cases.

Methods: We conducted a retrospective chart review of patients who came to the attention of infectious disease or neurology consultants or the microbiology laboratories at 7 hospitals in the municipalities of Toronto, Peel and Halton, Ont. Patients were included if they had been admitted to hospital or stayed overnight in the emergency department, had serological evidence of WNV infection and had clinical evidence of WNV fever, aseptic meningitis, encephalomyelitis or motor neuronopathy.

Results: In all, 64 patients met the inclusion criteria; 57 had encephalitis or neuromuscular weakness or both, 5 had aseptic meningitis, and 2 had WNV fever. The mean age was 61 years (range 26–87). The patients were predominantly active, middle-aged or elderly people living independently in the community. Seven patients were immunocompromised A febrile prodromal illness preceded the neurological symptoms in almost all cases. The most common neurological abnormality was decreased level of consciousness; this frequently evolved to severe lower motor neuron neuromuscular weakness. Ataxia and swallowing disorders were frequent and important problems. Sixteen patients (25%) required intubation and mechanical ventilation because of a decreased level of consciousness, inability to clear secretions or respiratory muscle weakness; 9 others had disabling muscle weakness of one or more limbs. Ten patients died. The study patients were in hospital a total of 1856 patient-days, including 532 patient-days in an intensive care unit. Only 28% (13/47) of the patients who survived encephalitis or neuromuscular weakness, or both, were discharged home without additional support. Slow turnaround time for serological test results resulted in delayed diagnosis.

Interpretation: The 2002 WNV infection outbreak in Ontario caused serious morbidity and mortality in the subset of patients who had encephalitis or neuromuscular weakness severe enough to require hospital admission.

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West Nile virus (WNV) infection has been described in endemic and epidemic forms throughout Africa and the Middle East since the 1930s.[1–6] It was first documented in North America in 1999, in New York City.[7,8] The total number of human cases in North America remained modest until 2002, when a 65-fold increase in the number was documented in the United States.[9] In 2001, WNV activity was detected in birds and mosquitoes in 12 health regions in southern Ontario, but no human disease was documented.[10] In 2002, WNV infection was detected in Ontario birds collected as early as May 19 in the Peel region.[11] Throughout the summer, increasing numbers of WNV-infected mosquitoes were detected, including those of the *Culex pipiens* species, which feed exclusively on birds, and numerous other mosquito species that have been implicated as secondary bridge vectors believed to have a major role in transmitting the virus to humans.[12,13] During August and September 2002 we encountered many patients admitted to hospital with a clinical syndrome compatible with WNV infection. We describe here the clinical characteristics of those cases.

Methods

Information on patients with WNV infection was collected through a collaboration of infectious diseases, microbiology, infection control and neurology staff at 7 Toronto-area hospitals (University Health Network, Mount Sinai Hospital, North York General Hospital, St. Joseph's Health Centre [Toronto], Credit Valley Hospital, Halton Healthcare Services – Oakville Trafalgar Site and

Sunnybrook & Women's College Health Sciences Centre). These hospitals accept 42% of acute care admissions in the 3 municipality areas (Toronto, Peel and Halton). Case finding was done through the infectious diseases and neurology consultation services and through hospital microbiology laboratories. Because of publicity before and during the WNV season, WNV serologic testing was included in the diagnostic workup of many patients with meningoencephalitis and peripheral neuropathy. However, active surveillance for human WNV infection was not done in 2002, so the complete extent of WNV activity is unknown.

The definitions used for this study are listed in Appendix 1. Patients were included if they were admitted to hospital or stayed overnight in the emergency department, had fever, had aseptic meningitis, encephalitis or neuromuscular weakness, and had serological evidence of WNV infection (4-fold increase in WNV antibodies assayed by hemagglutination inhibition, or a single titre of 1:320 or greater by hemagglutination inhibition and confirmed by plaque reduction neutralization assay). These inclusion criteria are a modification of the US Centers for Disease Control and Prevention (CDC) criteria[14] and of those described by Tardei and colleagues.[15] The hemagglutination inhibition and plaque reduction neutralization assays were performed as described previously.[16,17] Patients with a history of travel to arboviral endemic areas or of vaccination against yellow fever or Japanese encephalitis were included only if a 4-fold rise in flavivirus antibody levels was documented and the antibodies were confirmed to be WNV-specific by means of plaque reduction neutralization assay.

Using a standardized form, we obtained data by reviewing inpatient hospital charts and clinic charts (for follow-up visits) and by interviewing patients and their families. For calculation of length of hospital stay, data were censored after Dec. 19, 2002. For calculation of time to death, data were not censored after Dec. 19, because 2 of the deaths occurred after that date. The Karnofsky Performance Status Scale[18] was used to determine functional status before illness.

Results

Sixty-four cases of human WNV infection met the inclusion criteria. Illness onset occurred between Aug. 6 and Sept. 20, 2002, and peaked in the first week of September (Fig. 1). Patient characteristics are summarized in Table 1. The mean age was 61 years (median 62.5, range 26–87). Seven patients (11%) were immunocompromised. Thirty-two patients (50%) had significant underlying chronic medical conditions. Despite these underlying illnesses, 44 (72%) of the 61 patients for whom information on functional status was available had a Karnofsky score of 100 before their WNV illness. Only 6 patients (10%) had been unable to function independently before their illness (Karnofsky score ≤ 70), and no one had been a resident in a long-term care facility.

The symptoms and signs at presentation are listed in Table 2. The fever was usually high (mean peak temperature 39.3°C, median 39.1°C, range 37–40.5°C) and persisted after admission to hospital (mean duration 6 days, range 2–14). Myalgia was noted in 55% of the patients (26/47). Altered mental status and gastrointestinal symptoms were the most common localizing features. Clear evidence of meningeal involvement was often lacking: only 27% of the patients (17/64) had both headache and neck stiffness and 20% (13/64) had neither symptom. In 7 cases, the initial presentation was suggestive of sepsis, with fever, rigors, hypotension, tachycardia and tachypnea. One of these patients required inotropic support in the intensive care unit (ICU) during the first 2 days of admission. An erythematous macular or maculopapular rash was noted in 27% (17/64).

The admitting diagnoses were meningitis or encephalitis, or both, in 24 cases (38%), fever of unknown source in

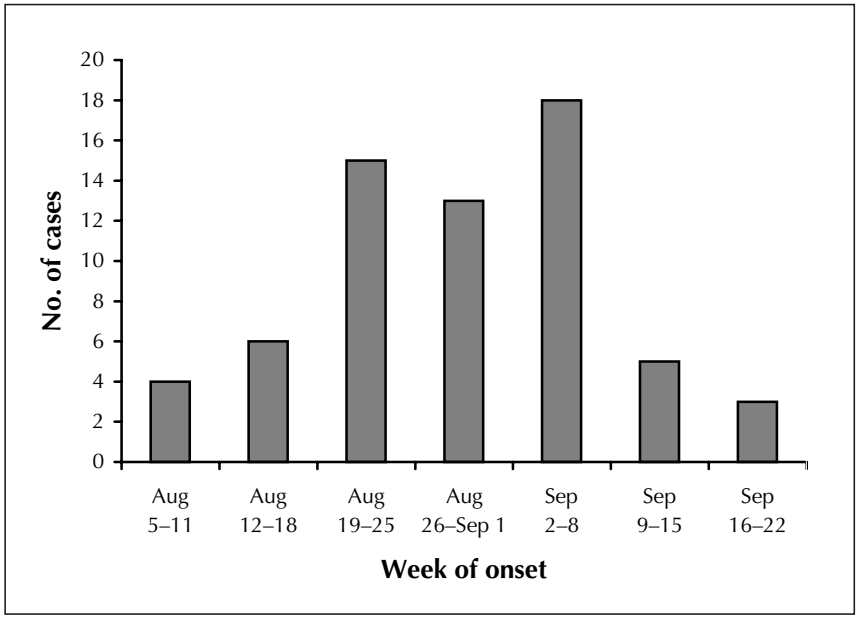

Fig. 1: Number of people with West Nile virus infection admitted to 7 Toronto-area hospitals in 2002, by week of onset.

19 (30%), bacterial infection such as pneumonia or pyelonephritis in 7 (11%), alcohol withdrawal in 3 (5%), stroke in 2 (3%), and myelopathy, multiple sclerosis and transverse myelitis in 1 case each (2%); information on the admitting diagnosis could not be discerned from the medical records in 6 cases (9%).

Neurological manifestations

Five patients had uncomplicated aseptic meningitis and 2 had WNV fever without neurological manifestations. The remaining 57 patients had meningoencephalitis or neuromuscular weakness, or both. Neurological dysfunction usually started several days after the onset of the systemic symptoms (fever, myalgia and gastrointestinal distress) and frequently evolved after admission to hospital. Table 3 presents the frequency of neurological symptoms and signs, and Fig. 2 illustrates the distribution of patients with various combinations of the 3 principal types of neurological manifestations (decreased level of consciousness, brainstem and cerebellar signs, and neuromuscular weakness).

Encephalitis was noted in 55 patients, 24 of whom also had neuromuscular weakness. Only 2 patients had weakness without signs of encephalitis (Fig. 2). Of the 55 cases of encephalitis, most (48) manifested as decreased level of consciousness (delirium in 21, stupor in 15 and coma in 12). Mental status changes persisted for a mean of 17 (median 10, range 1–67) days. In 15 (27%) of the 55 encephalitis cases, the clinical presentation was limited to a febrile illness with decreased level of consciousness. Other common neurological manifestations included dysphagia (22 patients), cerebellar ataxia (20) and neuromuscular weakness (26) (Table 3, Fig. 2). Less common neurological signs included facial weakness, ophthalmoplegia, dysarthria, nystagmus and myelopathy (Table 3). Cerebellar dysfunction was obvious at presentation in 15 of the 57 patients with neurological manifestations; it developed or became evident several days or weeks into the illness in 5 patients, often when the mental status returned to normal and the patient attempted to walk.

Four patients had severe brainstem disease with loss of brainstem reflexes, labile vital signs and features of "locked-in syndrome." Two of these patients were immunocompromised (one had undergone a liver transplantation and the other had had lymphoma treated with autologous stem-cell transplantation). In these 2 cases, T2-weighted and FLAIR (fluid-attenuated inversion recovery) MRI scans showed increased signal throughout the brainstem, thalami and vermis of cerebellum. Both patients died, and postmortem examination of one revealed marked inflammation in the grey matter of the thalami, basal ganglia, brainstem and cerebellum. Similar changes were found in the spinal cord grey matter, and there was destruction of anterior horn cells. The peripheral nervous system showed inflammation of the dorsal root ganglia and roots (radiculitis).

Neuromuscular weakness was present in 26 (46%) of the 57 patients with neurological manifestations and was documented days to weeks after the onset of systemic or central nervous system dysfunction. The clinical pattern of weak-

Table 1: Characteristics of 64 patients admitted to hospital because of West Nile virus (WNV) infection

Characteristic	No. (and %) of patients
Age group, yr	
20–29	2 (3)
30–39	6 (9)
40–49	7 (11)
50–59	14 (22)
60–69	11 (17)
70–79	17 (27)
≥ 80	7 (11)
Sex	
Male	36 (56)
Female	28 (44)
Immunocompromising condition	
Solid organ transplant recipient	3 (5)
Bone marrow transplant recipient	1 (2)
Cancer	1 (2)
Congenital myelodysplasia	1 (2)
Systemic vasculitis	1 (2)
Underlying condition	
Alcoholism	9 (14)
Diabetes mellitus	9 (14)
Heart disease	9 (14)
History of cancer	6 (9)
Cerebrovascular disease	5 (8)
Liver disease	1 (2)
Lung disease	1 (2)
Psychiatric illness	1 (2)
Renal failure	1 (2)

Table 2: Symptoms and signs at presentation

Symptom or sign	% (and no.) of patients
Fever	95 (61/64)
Altered mental status	75 (48/64)
Anorexia	84 (46/55)
Nausea	69 (40/58)
Vomiting	53 (31/58)
Headache and neck stiffness	
Yes	27 (17/64)
No	20 (13/64)
Diarrhea	34 (20/58)
Myalgia	55 (26/47)
Arthralgia	31 (15/48)
Rash	27 (17/64)
Lymphadenopathy	3 (2/64)

ness consisted of flaccid quadriparesis (17 patients), asymmetric paraparesis (6) and monoparesis (3). Satisfactory electromyography and nerve conduction studies were performed in 14 of the patients with weakness: anterior horn cell or motor axonal dysfunction was found in the majority (10/14). Three patients had mixed axonal degenerating and demyelinating processes, and 1 had a pure demyelinating process. The striking features in the patients with neuromuscular weakness were the extent of flaccid paralysis and the degree of muscle denervation shown on needle electromyography that suggested very pronounced anterior horn cell or motor axonal injury.

Cerebrospinal fluid (CSF) studies were performed in 56 cases: 4 had an elevated protein level, 4 had an elevated leukocyte count, and 48 had both an elevated protein level and pleocytosis. The CSF leukocyte count ranged from 0 to 1179 $\times$ 10^6/L, usually with a lymphocyte predominance (mean 60%, range 3%–100%), although polymorphonuclear leukocytes often predominated early. The mean CSF protein level was 0.9 (range 0.3–2.0) g/L. Six patients had abnormal lymphocytes in the CSF on cytological examination; this finding prompted investigation for lymphoma in 2, with negative results. A third patient, who had undergone lumpectomy and radiotherapy for localized breast cancer, was incorrectly diagnosed as having leptomeningeal carcinomatosis; the abnormal cells seen in her CSF were later shown to be reactive lymphocytes.

CT scans of the brain (in 58 cases) showed no acute abnormalities. MRI of the brain (in 24 cases) showed no acute changes except in the 2 immunocompromised patients described earlier. One other patient had MRI evidence of acute transverse sinus thrombosis.

Acute serologic testing for WNV infection was ordered a median of 2 days after admission (mean 4, range 0–18 days). In 24 cases (38%), WNV antibodies were not detected in the initial (acute) serum specimen. Three of the immunocompromised patients (organ transplant recipient, stem-cell transplant recipient, person with congenital myelodysplasia) had very delayed antibody responses: no response was detected at 25 days (2 patients) and 52 days (1 patient) after the onset of illness. Serum samples from these patients were tested again at 40, 58 and 74 days after illness onset, and high WNV antibody titres (≥ 1:320) were found.

Course in hospital

The patients were in hospital a total of 1856 patient-days, including 532 patient-days in an intensive care unit. The mean length of stay in hospital was 29 days (median 17, range 2 to more than 117 days). Nineteen patients (30%) were admitted to an ICU or a stepdown unit. Sixteen patients (25%) required mechanical ventilation because of a decreased level of consciousness, an inability to handle secretions or respiratory muscle paralysis. The mean length of stay in an ICU was 28 days (median 28, range 2 to more than 83 days [data censored after Dec. 19, 2002). The most common in-hospital complication was pneumonia (in 23% of patients [15/64]). Bacteremia devel-

Table 3: Neurological manifestations of WNV infection in 64 patients

Symptom or sign	No. (and %) of patients
Decreased level of consciousness	48 (75)
Neuromuscular weakness	26 (41)
Dysphagia	22 (34)
Ataxia	20 (31)
Dysarthria	11 (17)
Vertigo	9 (14)
Intention tremor	8 (13)
Diplopia or ophthalmoplegia	8 (13)
Facial weakness	7 (11)
Blurred vision	6 (9)
Dysdiadokinesis	5 (8)
Meningitis	5 (8)
Seizure	4 (6)
Incontinence	3 (5)
Tongue weakness	3 (5)
Myelopathy	2 (3)
Nystagmus	2 (3)
Parkinsonism	2 (3)
None	2 (3)

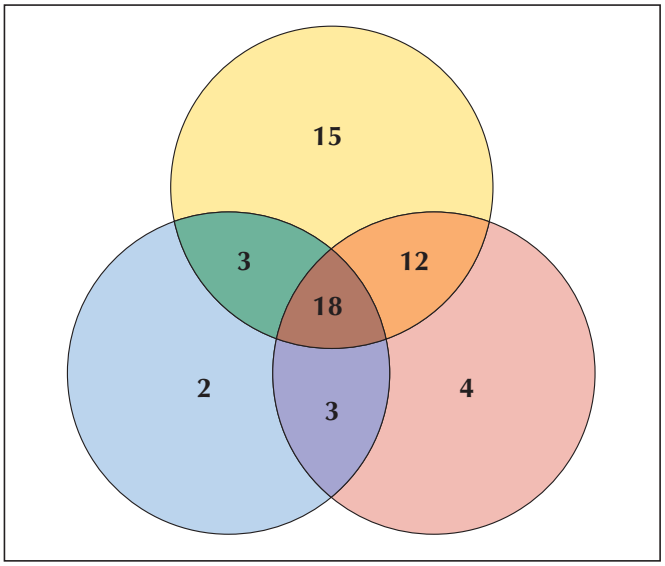

Fig. 2: Venn diagram, showing 3 principal types of neurological manifestations of West Nile virus infection: decreased level of consciousness (yellow circle), brainstem and cerebellar signs (pink circle) and neuromuscular weakness (blue circle). Most patients had abnormalities in all 3 areas (*n* = 18), decreased level of consciousness alone (*n* = 15) or a combination of decreased level of consciousness and brainstem/cerebellar signs (*n* = 12).

oped in 5 patients (8%), thromboembolic disease in 4 (6%), *Clostridium difficile* colitis in 3 (5%), myocardial infarction in 5 (8%) and acute renal failure (related to use of contrast agent for CT, blocked continuous bladder irrigation apparatus or medications) in 4 patients (6%).

The outcomes of the 57 patients with neurological manifestations of WNV infection were generally poor. Ten patients died, for a case-fatality rate of 18%. Death occurred a mean of 52 days after admission (range 3–128; data not censored after Dec. 19, 2002). In 8 cases it was attributed directly to one or both of WNV encephalitis or neuromuscular weakness with respiratory failure or aspiration; in the remaining 2 cases death was caused by WNV complicated by pulmonary embolism or sepsis resulting from prolonged hospital stay. Ataxia, weakness and cognitive dysfunction were persistent problems for survivors. At 30 days after the onset of illness, 4 of the 57 patients had died, 37 had persistent neurological deficits and 9 had recovered fully (data missing for 7 patients). The disposition of the 57 patients at discharge is presented in Table 4. Only 13 (23%) (or 28% of the 47 survivors) were discharged home without extra support; many were admitted to rehabilitation facilities or required extra support at home.

Interpretation

The 2002 outbreak of WNV in North America was the largest WNV outbreak ever documented and the largest arboviral outbreak in the Western hemisphere.[9] The patients in our series were predominantly active, middle-aged and elderly people living independently in the community. None had been in an institution before their WNV illness, and 72% had been functioning normally and independently (Karnofsky score of 100). Given the central role of mosquitoes in the transmission of WNV, it is intuitive that WNV infection would affect active, relatively healthy individuals, but this idea has not been emphasized in previous reports.[7,8,19] The care of the patients reported here was resource intensive, accounting for 1856 acute care hospital days, including 532 patient-days in ICU. This extent of care is an underestimate, because the data for hospital and ICU stays were censored after Dec. 19, 2002. Severe neuromuscular weakness led to prolonged mechanical ventilation in a few cases and weakness and disability in others. As a result, only 28% of those who survived WNV encephalitis or neuromuscular weakness were discharged home without extra support. The 10 deaths were attributed directly to WNV or to complications of prolonged hospital stay that would be expected in older, immobile, obtunded patients.

Pathological study of human autopsy material, including the autopsy reported here, and of primates infected with WNV shows that the virus produces encephalomyelitis of grey matter that involves the cerebral cortex, diencephalon, brainstem (including the cranial nerve nuclei) and the cerebellum.[20–23] Inflammation of the cranial nerve roots has also been reported.[23] The majority of patients with encephalitis in our series (65%) had clinical evidence of brainstem, cranial nerve or cerebellar disease, or a combination of these, ranging from dysphagia and ataxia to fatal necrotizing rhomboencephalitis. We believe that the clinical importance of brainstem and cerebellar disease with attendant swallowing disorders and ataxia may have been underemphasized in previous clinical reports.

The hallmark of WNV encephalitis is the combination of encephalopathy with lower motor neuron dysfunction owing to anterior horn cell disease or motor axonal neuropathy, or both. Pathological study of autopsy cases[23,24] and experimentally infected monkeys[21] suggests that inflammation in the anterior horns of the spinal cord,[21,23,24] with motor neuron dropout, is the cause of the characteristic motor neuronopathy. Our finding of nerve root inflammation suggests that this may also contribute to the motor neuronopathy responsible for the weakness. The flaccid paralysis syndrome was described in 1999[7,8] and again in 2002,[24–26] when concern was raised that patients were receiving inappropriate therapy aimed at Guillain–Barré syndrome for what was actually anterior horn cell disease or a nonimmune-mediated motor axonal neuropathy.[27] In our study, anterior horn cell disease occurred most frequently, but several cases had a combination of axonal and demyelinating neuropathy, and a single case had demyelination alone, which has occasionally been reported previously.[28–30] Because anterior horn cell disease causes such morbidity and mortality and is not amenable to the treatments used for Guillain–Barré syndrome, efforts must be focused on WNV disease prevention and determining whether agents such as WNV immune globulin[31,32] and interferon α-2b[33] prevent or attenuate the neurological disease.

The neurological complications of WNV infection most often occur in combination. However, flaccid paralysis, cerebellar or brainstem abnormalities and isolated movement disorders may occur in the absence of a decreased level of consciousness. The variety of neurological pictures we encountered is best represented by the Venn diagram in Fig. 2. Decreased level of consciousness frequently made it difficult or impossible to identify ataxia and neuromuscular weakness. The neurological findings often evolved after discharge from hospital. Therefore, it is important to per-

Table 4: Discharge disposition of 57 patients with neurological manifestations of WNV infection

Disposition	No. (and %) of patients
Dead	10 (18)
Home with extra support	14 (25)
Home without extra support	13 (23)
Transferred to rehabilitation institution	12 (21)
Moved in with relatives	4 (7)
Transferred to nursing home	2 (4)
In acute care facility	2 (4)

form regular follow-up neurological examinations after hospital admission, with particular emphasis on identifying evolving flaccid paralysis and swallowing disorders. CSF examination was useful in identifying meningeal inflammation and excluding other infectious agents. CNS imaging was helpful only in excluding other diagnoses. Serological testing is essential for establishing the diagnosis in individual patients and for timely surveillance of human WNV infection. In our series, the turnaround time for the hemagglutination inhibition assay was often 14 days, and additional time was required for confirmation with the plaque reduction neutralization assay. This delay caused diagnostic uncertainty in individual cases, prompted unnecessary empirical therapy or additional investigation, and delayed recognition of the extent of the WNV outbreak in Ontario. These problems call attention to the need to provide adequate resources for diagnostic laboratory support.

Previous reports have shown that the IgM capture enzyme-linked immunosorbent assay (ELISA) has a sensitivity of 95% and a specificity of 90% with serum specimens taken within 8 days after the onset of illness.[34] We need to determine whether this assay will provide an earlier diagnosis than the hemagglutination inhibition assay, which in our series yielded negative results with the first serum sample taken from 38% of the patients. The sensitivity of real-time polymerase chain reaction has been reported to be 55% with CSF samples and 10% with serum samples.[34] Our data suggest that the hemagglutination inhibition assay may not detect WNV infection for 2 weeks or more in some immunocompromised patients. Huang and associates[35] reported persistent viremia and absent antibody response (determined by means of IgM capture ELISA) in a patient with hematological malignant disease undergoing chemotherapy. Taken together, the results of these and other studies suggest that, in a subset of immunocompromised patients, antibody response is delayed and viremia is prolonged.[20,35,36] Therefore, we believe that the IgM capture ELISA should be complemented with nucleic acid amplification tests of CSF and serum samples to achieve the best diagnostic sensitivity early in the course of illness of immunocompromised patients.

The cases we have described emphasize the severe morbidity and mortality associated with WNV infection in the greater Toronto area in 2002. Although our study is limited by its retrospective nature and incomplete case ascertainment, the data provide strong support for an intensive, integrated surveillance and control program for the coming season. Improved and more timely diagnostic testing will be essential for WNV infection surveillance in humans, patient management and blood product screening.

This article has been peer reviewed.

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Appendix 1: Definitions

Altered mental state	Patient unable to communicate meaningfully and unable to perform activities of daily living because of altered level of consciousness or cognitive dysfunction.[37]
Aseptic meningitis	Fever, headache and clinical signs of meningismus or CSF pleocytosis in the absence of disturbance of consciousness. No bacterial growth in cultures of CSF or blood.[38]
Coma	Absent verbal, eye-opening or motor response to external stimulation.[37]
Delirium	Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention. Change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia. The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.[39]
Encephalitis	Fever, disturbance of consciousness and cerebrospinal fluid (CSF) changes compatible with inflammation. No bacterial growth from cultures of blood or CSF.[38]
Motor neuronopathy	Lower motor neuron dysfunction associated with muscle weakness and atrophy and motor axonal dysfunction on electrodiagnostic testing.
Myelopthy	Sensory or motor long tract disturbances attributable to spinal cord dysfunction, with or without segmental motor or sensory findings or sphincter impairment.
Peripheral neuropathy	Clinical or electrodiagnostic evidence, or both, of lower motor neuron and sensory dysfunction.
Stupor	State of impaired consciousness in which awareness of, and reactivity to, the environment is markedly diminished. Continuous stimulation is required to rouse the patient.[40]

Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: estimating the number of lives potentially saved through regionalization

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Abstract

Background: Previous research has shown that persons undergoing certain high-risk surgical procedures at high-volume hospitals (HVHs) have a lower risk of postoperative death than those undergoing surgery at low-volume hospitals (LVHs). We estimated the absolute number of operative deaths that could potentially be avoided if 5 major surgical procedures in Ontario were restricted to HVHs.

Methods: We collected data on all persons who underwent esophagectomy (613), colon or rectal resection for colorectal cancer (18 898), pancreaticoduodenectomy (686), pulmonary lobectomy or pneumonectomy for lung cancer (5156) or repair of an unruptured abdominal aortic aneurysm (AAA) (6279) in Ontario from Apr. 1, 1994, to Mar. 31, 1999. We calculated the excess number of operative deaths (defined as deaths in the period from the day of the operation to 30 days thereafter), adjusted for age, sex and comorbidity, among the 75% of persons treated in LVHs, as compared with the 25% treated in the highest-volume quartile of hospitals. Bootstrap methods were used to estimate 95% confidence intervals (CIs).

Results: Of the 31 632 persons undergoing any of the 5 procedures, 1341 (4.24%) died within 30 days of surgery. If the 75% of persons treated at the LVHs had instead been treated at the HVHs, the annual number of lives potentially saved would have been 4 (95% CI, 0 to 9) for esophagectomy, 6 (95% CI, 1 to 11) for pancreaticoduodenectomy, 1 (95% CI, –10 to 13) for major lung resection and 14 (95% CI, 1 to 25) for repair of unruptured AAA. For resection of colon or rectum, the regionalization strategy would not have saved any lives, and 17 lives (95% CI, 36 to –3) would potentially have been lost.

Interpretation: A small number of operative deaths are potentially avoidable by performing 4 of 5 complex surgical procedures only at HVHs in Ontario. In determining health policy, the most compelling argument for regionalizing complex surgical procedures at HVHs may not be the prevention of a large number of such deaths.

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Three decades of research has provided considerable support for the hypothesis that the outcomes of complex surgical procedures are better in hospitals where high volumes of similar operations are performed.[1–3] Some observers have advocated that certain procedures be performed only in high-volume hospitals (HVHs), at least within large metropolitan areas, where travel to HVHs is practical.[4,5] Controversy over the regionalization of complex surgical procedures in Canada is most notable in pediatric cardiac surgery,[6] cancer surgery[7,8] and adult coronary revascularization procedures.[9] Recent studies have suggested a substantial potential reduction in postoperative mortality through regionalization of major surgery at HVHs. Estimates of the potential number of lives saved per year include 4266 for 10 major surgical procedures in the United States Medicare program,[10] 602 for the treatment of 11 conditions in California[11] and 2581 for implementing the recommendation of the Leapfrog Coalition of employers in the United States[12] (which would permit employees to enrol only in health insurance plans practising "evidence-based referral").

The benefits of systematic attempts to regionalize major surgical procedures in Canada may not be as large as these studies suggest. Some studies of regionalization have included treatment of prevalent nonsurgical conditions, such as HIV infection.[11] In Canada, as compared with the United States, reduced competition among providers and single-payer funding of health care have already led to a significant amount of regionalization. We studied the potential benefit, in terms of lives saved from operative death (defined as death in the period from the day of the operation to 30 days thereafter), of performing 5 major surgical procedures in Ontario only at HVHs.

Methods

Data sources: We created cohorts of persons having 1 of 5 major surgical procedures in Ontario between Apr. 1, 1994, and Mar. 31, 1999, obtaining data from electronic databases maintained by the Canadian Institute for Health Information (CIHI) and the Ontario Registered Persons Database (RPDB). The CIHI database contains a record for each discharge from an acute-care hospital in Ontario. With the RPDB we determined the person's vital status 30 days after the surgical procedure. Data on the same individuals were linked between data sets by means of an anonymous unique identifier. This research was conducted with the ap-

proval of the Research Ethics Board of Sunnybrook and Women's College Health Sciences Centre.

Surgical procedures: We evaluated the potential impact of regionalization on the outcomes of 5 surgical procedures: esophagectomy, excision of a segment of colon or rectum for colorectal cancer, pancreaticoduodenectomy (the Whipple operation), lung lobectomy or pneumonectomy for lung cancer and repair of unruptured abdominal aortic aneurysm (AAA). We chose these procedures because they are complex, are associated with a nontrivial risk of operative death, are indicated when the patient's expectation of survival is longer than 1 or 2 months and are procedures for which regionalization based on hospital volume has been proposed.[13] We deliberately selected procedures that are uncommon and associated with a relatively high operative mortality (esophagectomy and pancreaticoduodenectomy), as well as procedures that are common and associated with a relatively low operative mortality (colon resection, major lung resection and AAA repair). For the cohort of persons having colon or rectal surgery or major lung resection, we included only those with a diagnosis of primary cancer. The codes used to identify procedures[14] and diagnoses[15] are listed in Table 1. The reliability of coding surgical procedures in the Ontario health databases is good, with 88% to 96% agreement between databases for procedures such as cholecystectomy and hysterectomy.[16]

Definition of hospital volume: Because some of the codes identifying hospitals changed during the study period owing to corporate restructuring, we identified hospitals using the code in effect during the fiscal year 1999. For each of the 5 procedures, we ranked the hospitals in order of their average annual volume. We then created hospital-volume categories that most uniformly divided the patients into 4 equal groups.[13] We defined HVHs as hospitals in which the highest quartile of subjects (with respect to average annual hospital volume) had their surgery; this category contained relatively few hospitals. This strategy provided a reasonable model for volume-based regionalization, in which the 75% of persons who ordinarily would not have had surgery at HVHs would be referred to 1 of these hospitals.

Statistical analysis: Trends in the crude risk of death across volume quartiles were evaluated with the Mantel–Haenszel chi-squared test.[17] The odds ratio for death associated with being in each of the 3 low-volume quartiles was estimated by fitting logistic regression models for each procedure cohort, in which the response variable was operative death (defined as the period from the day of the operation to 30 days thereafter), and the independent variables were hospital-volume category, age, sex and comorbidity. Our data sources did not contain information on cancer stage or person-level information on socioeconomic status. Comorbidity was represented in the regression models by a modified Charlson comorbidity score.[18,19] The score was calculated with the use of all diagnosis codes of the clinical modification of the *International Classification of Diseases*, 9th revision, for the index hospital admission in the CIHI data set, except for the code defined as the most responsible diagnosis. Age and comorbidity score were treated as continuous variables in multivariable models. To account for the prevalence of 30-day mortality, odds ratios were converted to relative risks.[20]

The number of excess deaths within each of the low-volume quartiles was estimated by multiplying the excess risk of death associated with being in this quartile by the number of subjects in the quartile and by the baseline risk of death in the high-volume category. The total annual number of potentially avoidable deaths was the sum of the number of excess deaths in each of the 3 low-volume quartiles, averaged over the 5-year study period and rounded up to the nearest integer (a more negative integer was used for negative numbers). Using bootstrap methods[21] we estimated 95% confidence intervals (CIs) around estimates of the number of lives potentially saved. For each cohort, we generated 1000 sample data sets (of sample size equal to the number of persons in the cohort) by doing repeated random sampling of the entire cohort. We estimated the potential number of lives saved for each sample data set and used the 2.5th and 97.5th percentiles of the resulting distribution to represent, respectively, the lower and upper 95% confidence limits.

Results

During the 5-year period of the study 31 632 persons in Ontario had 1 of the 5 procedures (or procedure-diagnosis combinations). Characteristics of the study subjects according to hospital-volume quartile are presented in Table 2. The mean age was lowest among those having pancreaticoduodenectomy and highest among those having repair of unruptured AAA. For all procedures, there were more males than females. The procedure with the largest male preponderance was AAA repair; in contrast, the proportion of male subjects having colon or rectal surgery was only slightly greater than half. Charlson comorbidity scores were highest for persons who had an esophagectomy and lowest for those who had an AAA repair.

Table 1: Procedure and diagnosis codes used to define the study cohorts

Procedure	CCP procedures codes	ICD-9 diagnosis codes
Esophagectomy	54.33	
Resection of colon or rectum for colorectal cancer	57.52–57.56, 57.59, 60.4, 60.51, 60.52	153.0–153.8, 154.0, 154.1
Pancreaticoduodenectomy	64.6	
Major lung resection for lung cancer	44.4, 44.5	162.3–162.5, 162.8, 162.9
Repair of unruptured abdominal aortic aneurysm (AAA)	50.24, 50.34, 50.54, 51.25	441.4, 441.9

Note: CCP = Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures,[14] ICD-9-CM = International Classification of Diseases, 9th revision, clinical modification.[15]

The number of hospitals at which the procedures were done during the study period varied according to the procedure. Esophagectomy was performed at 47 hospitals, resection of the colon or rectum at 134, pancreaticoduodenectomy at 49, major lung resection at 54 and repair of unruptured AAA at 57. The number of hospitals in each volume stratum and the average annual volumes for each hospital are listed in Table 2. The highest average annual volumes ranged from 19.0 for esophagectomy to 149.8 for resection of the colon or rectum.

Of the subjects, 1341 (4.24%) died within 30 days of surgery. The 30-day mortality rate ranged from 3.8% for resection of the colon or rectum to 13.4% for esophagectomy. The crude and adjusted risks of death within 30 days according to quartile of average hospital volume are presented in Table 3. Point estimates of the relative risk at low-volume hospitals, adjusted for age, sex and comorbidity, were greater than 1.0 for each of the low-volume quartiles for all procedures except the 3 low-volume quartiles for resection of the colon or rectum and the third quartile for major lung resection.

The annual number of lives potentially saved by regionalization at HVHs was 4 (95% CI, 0 to 9) for esophagectomy, 6 (95% CI, 1 to 11) for pancreaticoduodenectomy, 1

Table 2: Characteristics of persons undergoing any of 5 surgical procedures in Ontario hospitals from 1994 to 1999, according to hospital-volume quartile

	Average annual hospital volume			
Procedure and variables*	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Esophagectomy				
No. of subjects	161	167	108	177
No. of hospitals	37	6	2	2
Average annual volume	2.8	8.8	16.6	19.0
Mean age (and SD), yr	65.2 (10.2)	63.7 (10.0)	65.0 (10.9)	63.4 (11.6)
% male	69.6	73.7	73.2	76.8
Mean Charlson score (and SD)	3.9 (2.2)	4.5 (2.2)	4.4 (2.2)	4.0 (2.3)
Resection of colon or rectum for cancer				
No. of subjects	4817	4873	4770	4438
No. of hospitals	89	23	14	8
Average annual volume	33.6	52.8	87.4	149.8
Mean age (and SD), yr	69.5 (11.1)	68.6 (11.7)	68.7 (11.6)	68.4 (11.8)
% male	52.8	55.7	54.2	53.0
Mean Charlson score (and SD)	2.0 (2.7)	2.1 (2.8)	2.4 (2.9)	2.5 (2.9)
Pancreaticoduodenectomy				
No. of subjects	209	139	157	181
No. of hospitals	36	7	4	2
Average annual volume	2.8	5.4	11.4	24.8
Mean age (and SD), yr	63.0 (10.6)	62.7 (12.0)	62.2 (12.8)	62.7 (11.9)
% male	56.9	58.3	56.7	53.6
Mean Charlson score (and SD)	1.7 (2.5)	1.6 (2.4)	2.0 (2.7)	3.1 (2.9)
Major lung resection for cancer				
No. of subjects	1442	1155	1439	1120
No. of hospitals	40	8	4	2
Average annual volume	18.2	45.0	86.0	129.4
Mean age (and SD), yr	65.2 (9.5)	65.8 (9.4)	64.6 (9.9)	65.0 (9.6)
% male	58.8	59.2	60.7	55.2
Mean Charlson score (and SD)	1.7 (2.5)	2.4 (2.8)	2.3 (2.7)	3.0 (3.0)
Repair of unruptured AAA				
No. of subjects	1679	1580	1902	1118
No. of hospitals	39	10	6	2
Average annual volume	21.8	42.0	92.8	130.0
Mean age (and SD), yr	70.5 (7.2)	70.6 (7.3)	71.0 (7.5)	70.7 (7.5)
% male	82.9	81.0	82.4	83.3
Mean Charlson score (and SD)	0.6 (0.9)	0.5 (0.8)	0.5 (0.9)	0.5 (0.9)

Note: SD = standard deviation.
*Average annual volume is that of the highest-volume hospital in the quartile. The Charlson score was calculated with the use of secondary diagnosis codes on the hospital-discharge record for the surgical procedure.

Table 3: Risk of death within 30 days of the surgery,* according to hospital-volume quartile

Procedure and variables†	Average annual hospital volume				*p* value for trend‡
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Esophagectomy					
No. of subjects	161	167	108	177	
No. of deaths	30	21	13	18	
Risk of death (%)	18.6	12.6	12.0	10.2	0.03
Adjusted relative risk of death (and 95% CI)	1.9 (1.0, 3.7)	1.3 (0.6, 2.5)	1.1 (0.5, 2.4)	1.0	0.04
Resection of colon or rectum for colorectal cancer					
No. of subjects	4817	4873	4770	4438	
No. of deaths	181	181	159	192	
Risk of death (%)	3.8	3.7	3.3	4.3	0.32
Adjusted relative risk of death (and 95% CI)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	0.8 (0.6, 0.9)	1.0	0.54
Pancreaticoduodenectomy					
No. of subjects	209	139	157	181	
No. of deaths	24	14	17	11	
Risk of death (%)	11.5	10.1	10.8	6.1	0.10
Adjusted relative risk of death (and 95% CI)	2.2 (1.0, 4.7)	1.9 (0.8, 4.4)	2.0 (0.9, 4.6)	1.0	0.08
Major lung resection for lung cancer					
No. of subjects	1442	1155	1439	1120	
No. of deaths	65	61	40	49	
Risk of death (%)	4.5	5.3	2.8	4.4	0.20
Adjusted relative risk of death (and 95% CI)	1.2 (0.8, 1.7)	1.3 (0.8, 1.8)	0.7 (0.4, 1.0)	1.0	0.07
Repair of unruptured AAA					
No. of subjects	1679	1580	1902	1118	
No. of deaths	81	85	63	36	
Risk of death (%)	4.8	5.4	3.3	3.2	< 0.01
Adjusted relative risk of death (and 95% CI)	1.5 (1.0, 2.2)	1.8 (1.2, 2.8)	1.0 (0.7, 1.5)	1.0	< 0.01

Note: CI = confidence interval.
*Defined as the period from the day of the operation to 30 days thereafter.
†The adjusted relative risk of death represents a prevalence-corrected multivariate odds ratio, adjusted for age, sex and comorbidity. The referent category was Quartile 4 (with the highest volume).
‡The *p* value for the trend in the crude risk of death across the hospital-volume quartiles is for the Mantel–Haenszel χ-squared test with 1 degree of freedom. The *p* value for the trend in the adjusted risk of death across hospital-volume quartiles is for the Wald χ-squared test of the hospital-volume term in a logistic regression model with 30-day mortality as the dependent variable and age, sex, comorbidity score and a single term for hospital-volume quartile (coded on an integer unit scale) as the independent variables.

Table 4: Annual number of potentially avoidable deaths within 30 days of the surgery that would be attributable to regionalization of the 5 surgical procedures at high-volume hospitals* in Ontario

Procedure	No. of persons	No. of deaths	Risk of death, %	Potentially avoidable deaths (per year)†	
				Point estimate (and 95% CI‡)	% of all deaths (and 95% CI)
Esophagectomy	613	82	13.4	4 (0, 9)	24.3 (0, 54.9)
Resection of colon or rectum for colorectal cancer	18 898	713	3.8	–17 (–36, 3)	–11.9 (–25.2, 2.1)
Pancreaticoduodenectomy	686	66	9.6	6 (1, 11)	45.5 (7.6, 83.3)
Major lung resection for lung cancer	5 156	215	4.2	1 (–10, 13)	2.3 (–23.3, 30.2)
Repair of unruptured AAA	6 279	265	4.2	14 (1, 25)	26.4 (1.9, 47.2)

*Defined as hospitals caring for the 25% of patients who had their procedures at the hospitals with the highest procedure volumes, volumes being categorized according to the distribution of patients by average annual hospital volume of similar procedures within the study period.
†Estimated by multiplying the excess risk of death in each of the 3 lower-volume quartiles by the number of subjects in the quartile and the risk of death within 30 days in the highest hospital-volume quartile, averaged over the 5-year study period and rounded up to the nearest integer.
‡Nonparametric 95% confidence limits were defined as the 2.5th and 97.5th percentiles of the distribution of estimates generated by 1000 bootstrap resamplings of the data set for each procedure cohort.

(95% CI, –10 to 13) for major lung resection and 14 (95% CI, 1 to 25) for repair of unruptured AAA (Table 4). For resection of colon or rectum, however, there would be 17 (95% CI, 36 to –3) lives potentially lost because of regionalization at HVHs.

Interpretation

A major impetus for the regionalization of complex surgical procedures at HVHs is the belief that many postoperative deaths would be prevented if more people had their surgery at HVHs. We found that for some complex surgical procedures a policy of restricting certain types of surgery to HVHs could indeed result in fewer deaths during or shortly after surgery. However, the number of potentially avoidable deaths each year is small: between 1 and 14 for 4 of the procedures that we evaluated. Our data suggest that there would be no such benefit to regionalizing resection of the colon or rectum for cancer at HVHs in Ontario.

Compared with other studies of the benefit of volume-based regionalization,[10–12] our study did not identify potential for a large reduction in the number of operative deaths. Possible explanations are that we did not consider medical interventions aside from major surgical procedures, we evaluated only 5 procedures, and the population of Ontario is substantially smaller than that of the geographic areas of the other studies. Further, it is likely that surgical procedures are already relatively regionalized in Ontario as compared with areas of the United States. For example, coronary revascularization procedures (percutaneous transluminal coronary angioplasty and coronary-artery bypass grafting) were done in 25% of the hospitals caring for persons with myocardial infarction in the United States in 1991, as compared with only 3% of similar hospitals in Ontario.[22] If complex surgical procedures have already been effectively regionalized, measures to promote further regionalization will have less incremental benefit.

The results of this study must be interpreted with caution, since we made several important assumptions in estimating the effect of volume-based regionalization. We assumed a cause-and-effect association between hospital volume and outcome, that persons sent to HVHs because of regionalization would have the same risk of death as other persons having surgery at HVHs and that regionalization at HVHs is feasible for all persons. To the extent that these assumptions are unrealistic, their bias would be towards an increased benefit of regionalization. We looked only at 30-day mortality and not in-hospital mortality or mortality over a different period, such as 60 days.[23–25] Our data sources did not contain information on cancer stage or socioeconomic indicators, which are important determinants of prognosis. We did not evaluate outcomes other than short-term mortality, such as long-term survival after cancer surgery or limb ischemia after AAA repair. Therefore, we cannot exclude a more substantial benefit of regionalization for outcomes that may be more sensitive measures of the quality of surgical care.

What do our findings say about the potential value of regionalizing complex surgery at high-volume centres? First, our data suggest that the value of volume-based regionalization should be carefully studied before major policy initiatives are undertaken. The absolute health benefits of regionalization must be better quantified and should be weighed against potential drawbacks, such as patient preference for local care[26] and the impact on the delivery of rural health care.[4] Second, the benefit of regionalization is condition-specific and in general will be larger for procedures that are common, have a high mortality risk or have a strong association between volume and outcome. Third, further research should focus on the determinants of poor outcomes, such as short-term mortality, in lower-volume hospitals. If volume-based regionalization becomes impractical or impossible as a policy measure, then quality-improvement initiatives will necessarily be directed towards improving structures and processes of care at institutions with poorer outcomes. Finally, it is important to study outcomes other than short-term mortality in assessing the quality of surgical care. There may be good reasons for volume-based regionalization of certain complex surgical procedures; however, the perception that the main benefit of regionalization is a substantial reduction in postoperative mortality may be erroneous. Rather, the benefits of improved care might be better identified by using more sensitive and specific measures of the quality of care, such as long-term survival after cancer surgery, cancer-free survival or health-related quality of life, or procedure-specific outcomes such as renal dysfunction following AAA repair.

In conclusion, we found that under assumptions favouring the feasibility of regionalization, a small number of operative deaths are potentially avoidable by restricting 4 of the 5 complex surgical procedures we studied to HVHs. In determining health policy, the most compelling argument for regionalizing complex surgical procedures at these centres may not be the prevention of a substantial number of postoperative deaths.

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Identification and containment of an outbreak of SARS in a community hospital

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ß See related articles pages 1432 and 1434

Abstract

Background: Severe acute respiratory syndrome (SARS) is continuing to spread around the world. All hospitals must be prepared to care for patients with SARS. Thus, it is important to understand the transmission of this disease in hospitals and to evaluate methods for its containment in health care institutions. We describe how we cared for the first 2 patients with SARS admitted to our 419-bed community hospital in Richmond Hill, Ont., and the response to a SARS outbreak within our institution.

Methods: We collected clinical and epidemiological data about patients and health care workers at our institution who during a 13-day period had a potential unprotected exposure to 2 patients whose signs and symptoms were subsequently identified as meeting the case definition for probable SARS. The index case at our hospital was a patient who was transferred to our intensive care unit (ICU) from a referral hospital on Mar. 16, 2003, where he had been in close proximity to the son of the individual with the first reported case of SARS in Toronto. After 13 days in the ICU, a diagnosis of probable SARS was reached for our index case. Immediately upon diagnosis of our index case, respiratory isolation and barrier precautions were instituted throughout our hospital and maintained for a period of 10 days, which is the estimated maximum incubation period reported for this disease. Aggressive surveillance measures among hospital staff, patients and visitors were also maintained during this time.

Results: During the surveillance period, 15 individuals (10 hospital staff, 3 patients and 2 visitors) were identified as meeting the case definition for probable or suspected SARS, in addition to our index case. All but 1 individual had had direct contact with a symptomatic patient with SARS during the period of unprotected exposure. No additional cases were identified after infection control precautions had been implemented for 8 days. No cases of secondary transmission were identified in the 21 days following the implementation of these precautions at our institution.

Interpretation: SARS can easily be spread by direct personal contact in the hospital setting. We found that the implementation of aggressive infection control measures is effective in preventing further transmission of this disease.

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Severe acute respiratory syndrome (SARS) is a newly recognized illness associated with infection from a novel coronavirus.[1–3] The first case of SARS in Canada was diagnosed in Toronto on Mar. 13, 2003.[4] As of Apr. 24, 2003, 140 probable and 187 suspect cases of SARS had been reported in Canada,[5] most in Toronto and surrounding communities. The virus has now been transmitted through 4 generations of cases in Canada.

York Central Hospital is a community hospital in Richmond Hill, Ont., in the Toronto area. It is a 419-bed facility with 219 acute care beds, 52 chronic care beds, 32 rehabilitation beds and 116 long-term care beds. There are over 1800 hospital staff, 300 physicians and 800 volunteers affiliated with this institution.

Between Mar. 16 and Mar. 28, 2003, there was unprotected exposure to 2 patients at our institution who were subsequently found to meet the epidemiological criteria for probable SARS.[6] On Mar. 16, 2003, a 77-year-old man who required urgent hemodialysis was transferred from Scarborough Hospital, Grace Division, in Toronto to the intensive care unit of York Central Hospital. At the time of transfer, it was not known that the patient had been exposed to the SARS virus at the referring institution, thus, no specific respiratory isolation precautions were used. After he had spent 13 days in intensive care, the diagnosis of SARS was made.

On March 21, the wife of the first patient was also admitted to York Central Hospital and stayed there until March 26. Her presenting complaints were chest pain and dyspnea. She also had exposure to the SARS virus while visiting her husband at the referring hospital and while visiting her husband in intensive care during the period of unprotected exposure to the SARS virus at York Central Hospital. She was transferred to a nursing home for respite care on March 26. On March 29 she was readmitted to York Central Hospital with persisting respiratory symptoms. Because of the patient's history of direct contact with a probable SARS case (her husband), she was immediately placed in respiratory isolation and transferred to our SARS Assessment and Treatment Unit (SATU) upon her arrival.

We describe the hospital-wide infection control procedures that were used to prevent the further transmission of

SARS within our hospital and the greater community and the clinical outcomes of the subsequent 14 cases of SARS that we managed.

Methods

Because of uncertainty pertaining to the infectivity of the SARS virus at the time our first patient was identified as having probable SARS, it was assumed that all individuals who had visited or were working at York Central Hospital during the 13-day period from Mar. 16 to Mar. 28, 2003, had potential unprotected exposure to the SARS virus. All of these individuals were instructed to enter a voluntary quarantine of 10 days from their last exposure to the hospital under the directive of the Regional Public Health Unit and the SARS Provincial Operations Centre for the Ontario Ministry of Health and Long-Term Care. All hospital employees and volunteers were contacted by telephone and told about the quarantine requirements. A list of all patients admitted, discharged, transferred or deceased who were at York Central Hospital between March 16 and March 28 was provided to the Provincial Operations Centre who then had the local public health units contact the relevant individuals, informing them of the quarantine directives. The news media were also used to facilitate the dissemination of this information.

Asymptomatic hospital staff were allowed to continue working at York Central Hospital during the quarantine period, but were prohibited from working at other institutions. All hospital staff and visitors were required to complete a SARS screening questionnaire[7] before being permitted to enter the building. The screening process occurred outside the hospital's entrance in a heated tent that was erected specifically for this purpose. A pool of the hospital's nursing staff reviewed each person's responses on the questionnaire and took his or her temperature. Individuals who did not pass the screening questionnaire were referred to either the hospital's emergency department or to the occupational health department.

All individuals who entered the hospital were required to use full respiratory precautions consisting of gowns, gloves and N95 respirator masks during the hospital's 10-day quarantine period.

Two of the authors (H.D. and H.H.) interviewed patients regarding epidemiological risks and potential exposures to other patients and institutions affected by SARS. Potential occupational exposures for hospital employees were cross-referenced with employee work schedules. Physicians caring for patients with SARS at other Toronto area hospitals were surveyed by email for possible SARS-related admissions that were associated with the period of unprotected exposure at our hospital. The charts of all probable and suspect SARS cases treated at York Central Hospital were reviewed by 2 of the authors (H.D. and H.H.).

Because of quarantine constraints, ethics approval was obtained from the hospital's research committee by communication with committee members by electronic means. Written informed consent for the release of medical information for use in this study was obtained from all patients.

Case descriptions

Patient 1

Patient 1, a 77-year-old man, was transferred to York Central Hospital's intensive care unit from Scarborough Hospital, Grace Division, in Toronto for emergency hemodialysis, a service that was not available at the referring hospital. His past medical history was significant for type 2 diabetes mellitus, coronary artery disease, congestive heart failure and chronic renal failure. He had no recent travel history. Patient 1 was first admitted at the referring hospital on Mar. 7, 2003, and remained there until Mar. 10, 2003, for the treatment of congestive heart failure (Fig. 1). It was during this admission that patient 1, while in the emergency department of the referring hospital on March 7, had an unprotected exposure to another patient in the same treatment area who was subsequently identified as having probable SARS (Dr. David Rose, Scarborough Hospital, Grace Division, Toronto, Ont.: personal communication, Apr. 23, 2003).[4] He returned to the emergency department of the referring hospital on March 14 with fever, dyspnea and pulmonary infiltrates. Recurrent congestive heart failure and pneumonia were diagnosed, and the patient was started on intravenous levofloxacin. He developed further deterioration in his renal function and respiratory status and was started on noninvasive positive-pressure ventilation (NIPPV). He was transferred to York Central Hospital on March 16, while on NIPPV for urgent hemodialysis for his acute respiratory and renal failure. On Mar. 17, 2003, his antibiotics were changed to intravenous ceftriaxone and intravenous azithromycin. Patient 1 was intubated on Mar. 18, 2003, for worsening respiratory failure consistent with acute respiratory distress syndrome. He remained febrile for 5 days until March 18. The condition of patient 1 continued to deteriorate, leading to progressive multi-organ dysfunction. He was started on intravenous methylprednisolone, 40 mg every 12 hours, on March 23 for unresolving acute respiratory distress syndrome. A pulmonary artery catheter was inserted on Mar. 25, 2003, demonstrating a pulmonary capillary wedge pressure (PCWP) of 15 mm Hg, while the patient received 18 cm H_2O of positive end-expiratory pressure (PEEP) from the ventilator. Because of increasing concern regarding the number of SARS cases at the referring hospital, patient 1 was placed in respiratory isolation on March 27. He was not prescribed ribavirin therapy, because it was felt that antiviral medication would have limited effectiveness, given that the patient had had progressive symptoms for 2 weeks. On Mar. 29, 2003, patient 1 died of multi-organ failure. No autopsy was performed.

Patient 2

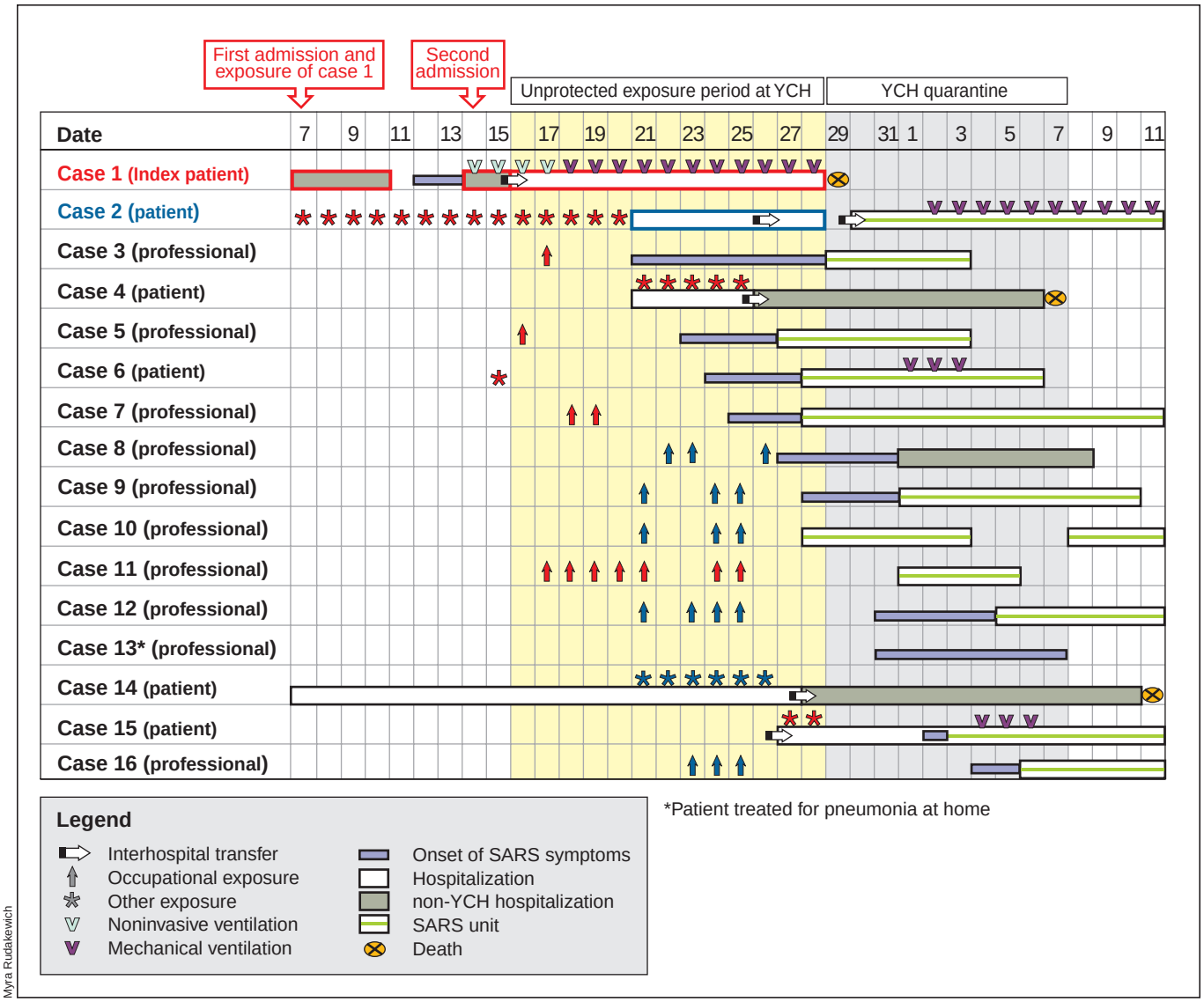
Patient 2, a 77-year-old woman, was the spouse of patient 1. She presented to York Central Hospital's emergency department on Mar. 21, 2003, with chest discomfort, fever (38.4°C) and dyspnea. Her past medical history was significant for atrial fibrillation, transient ischemic attack and osteoarthritis. Her chest radiograph demonstrated a 10% apical pneumothorax of the right lung with bilateral pulmonary infiltrates. She was admitted to the general surgery service for management of her pneumothorax, which was treated conservatively, without surgical intervention. She was then transferred to a nursing home on March 26, because her husband could not take care of her. On March 29, patient 2 was readmitted to York Central Hospital's SATU due to concern regarding her potential exposure to the first index case and persisting dyspnea. She had worsening respiratory failure, with the development of acute respiratory distress syndrome requiring orotracheal intubation and mechanical ventilation on Apr. 2, 2003. Bronchiolar lavage identified only normal respiratory flora. On Mar. 29, 2003, ribavirin therapy was started with a 2-g intravenous bolus, then 1 g intravenously every 6 hours for 4 days and then 500 mg intravenously every 8 hours for 6 days. On Mar. 30, 2003, she was

started on systemic corticosteroids with intravenous methylprednisolone, 40 mg every 12 hours. She was successfully extubated after 10 days of mechanical ventilation and remains in hospital, as of April 24.

Results

Upon recognition of the unprotected exposure to the SARS virus at our hospital, respiratory isolation and barrier precautions were implemented throughout our hospital at 1800 hours on Mar. 28, 2003. Infection control measures and organizational interventions in restricting hospital access were implemented and the SATU was set up based on directives from the SARS Provincial Operations Centre of the Ontario Ministry of Health and Long-Term Care (Fig. 2).

The dedicated 15-bed SATU was created on a separate medical ward. This was accomplished within 24 hours. The ward had previously been empty as part of our hospital's ongoing expansion and redevelopment. The ventilation system for this ward was isolated from the rest of the hospital. The entire unit was kept at negative pressure relative to the hospital by 2 externally vented 1000-cfm exhaust fans. Each of the private patient rooms was maintained at a negative pressure relative to the corridor by externally vented 270-cfm HEPA (high efficiency particulate air) air filters. Appropriate monitoring equipment was used to allow for the care of critically ill and mechanically ventilated patients with SARS in the SATU. A dedicated team of physicians, nurses and other al-



Myra Rudakewich

Fig. 1: Timeline of the SARS outbreak at York Central Hospital (YCH), Richmond Hill, Ont., from Mar. 7, 2003, to Apr. 11, 2003. The period of unprotected exposure extends from the admission of the first SARS case to YCH on Mar. 16, 2003, to the implementation of hospital-wide respiratory isolation and barrier precautions. That index patient's exposure and first and second admission to hospital were at Scarborough Hospital, Grace Division, Toronto.

lied health care providers provided care to the patients on the SATU. Using an approach similar to that taken at Mount Sinai Hospital[8] in Toronto, staff members for the SATU were recruited from the intensive care unit and the medical–respiratory ward for their expertise in the treatment of both critically ill patients and patients requiring respiratory isolation. In order to limit the number of physicians working in both the SATU and other areas of the hospital, a weekly call roster assigned all patients admitted to the SATU to a single attending physician. Two critical care physicians provided 24-hour attending physician coverage for the SATU. Two additional critical care physicians provided additional support in the management of mechanically ventilated SARS patients on the SATU. The follow-up of recovered SARS patients discharged from hospital was performed in accordance with the World Health Organization (WHO) guidelines.[9]

Ten hospital staff members who met the case definition for either probable or suspect SARS were identified (Table 1).[6] The SARS screening tool identified 3 of the 10 hospital staff when they arrived at work. Four hospital staff had direct personal contact with patient 1 during the period of unprotected exposure. Five hospital staff had direct personal contact with patient 2 during the period of unprotected exposure. One hospital employee (case 13) had no identifiable direct contact with either patient, but was working at the hospital during the period of unprotected exposure and met the clinical criteria for probable SARS.

Four patients were identified who met the case definition for either probable or suspect SARS. Two hospital patients were exposed to patient 1 while in the intensive care unit before the implementation of hospital-wide respiratory precautions. One patient had shared the same room as patient 2 during the period of unprotected exposure. Another patient (case 6) was a visitor at the referring hospital for patient 1 on Mar. 15, 2003, where she was visiting a patient in the same cardiac care unit where patient 1 was being treated.

Of the 15 cases with probable or suspect SARS associated with our index patient, 11 were admitted to the SATU, 3 were treated at other hospitals and 1 was treated at home. Nine of the 11 cases admitted to the SATU have since been discharged home. No further cases of probable or suspect SARS related to the 13-day period of unprotected exposure were identified in the 10 days following the hospital-wide quarantine period, which ended on Apr. 7, 2003.

Interpretation

The initial public health response to the SARS outbreak within our hospital involved the mass voluntary quarantine of over 5000 people.[10] The rationale for this action was the

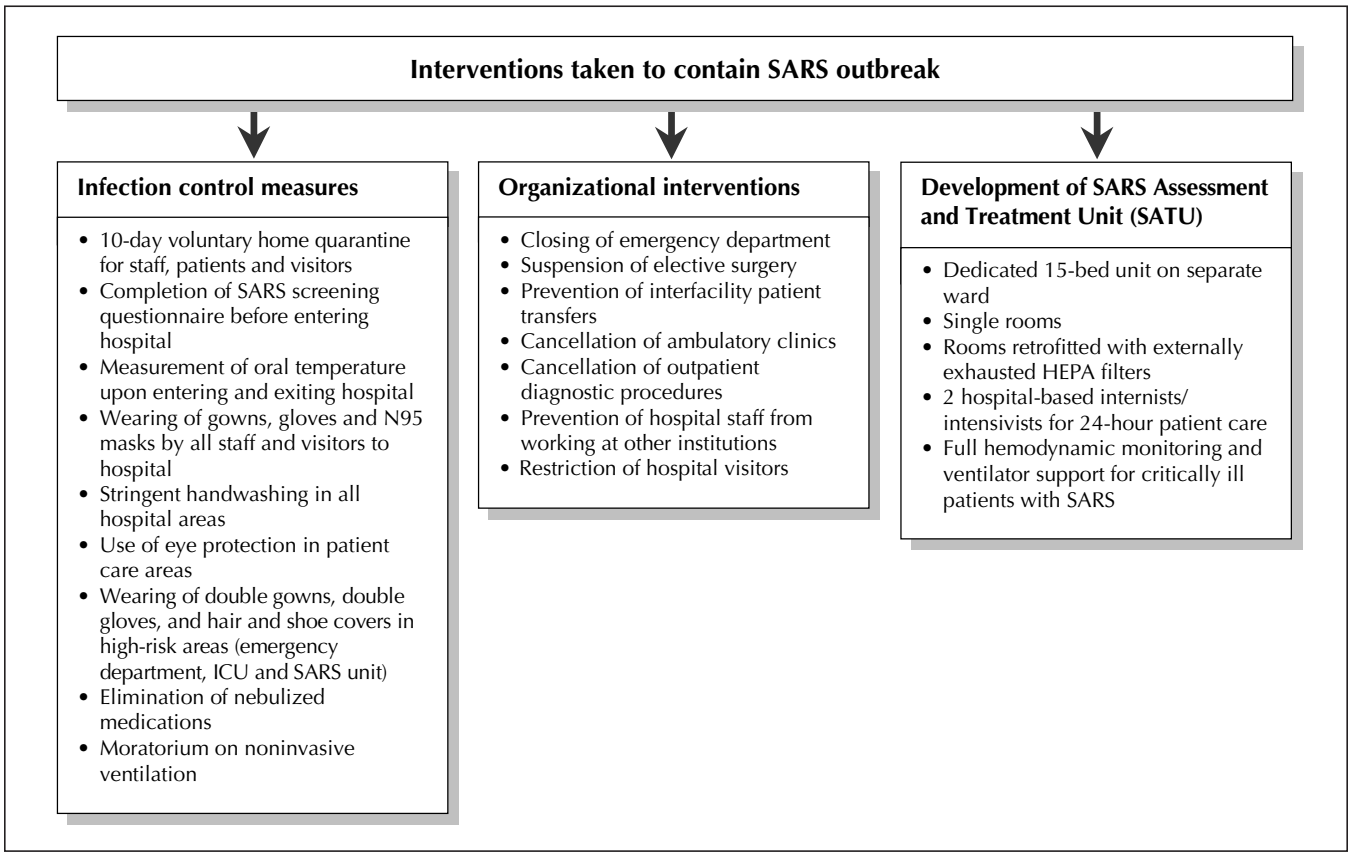


Fig. 2: Interventions taken to contain a SARS outbreak at York Central Hospital, Richmond Hill, Ont. SARS = severe acute respiratory syndrome, ICU = intensive care unit, HEPA = high efficiency particulate air.

hypothesis that our hospital was "grossly contaminated" during the period of unprotected exposure. The quarantine measures affected over 1800 hospital staff, 225 physicians, 170 neighbouring high school students who use the hospital cafeteria and hundreds more volunteers, patients and visitors. There was also tremendous disruption to the community's ability to access acute medical care services. The vast majority of SARS cases identified in this study had clearly identifiable direct personal contact with a symptomatic probable SARS patient. In only 1 of the 15 cases identified was there no identifiable period of close contact with a probable SARS patient. Although this case did meet the case definition for probable SARS, the clinical course was different from the other SARS cases and, in the opinion of the authors, this individual probably did not have SARS at all.

Our knowledge about the natural history, diagnosis and treatment of SARS grows each week. In retrospect, many of the treatments that are commonly used in the acute management of respiratory disease may have actually facilitated the transmission of the SARS coronavirus.[11] The index patient at our hospital and the index patient at the referring hospital to whom he was exposed were both treated with NIPPV.[4] The use of NIPPV and nebulized medications should be avoided in SARS patients.

There are several limitations to our study. Due to the still uncertain natural history of this disease, it is conceivable that patients with subclinical or very mild disease may not have been identified by the screening tool (e.g., patients without fever or cough). The opportunity for transmission of SARS by such patients would have been prevented by

Table 1: Characteristics of 16 hospital staff and patients associated with the SARS outbreak at York Central Hospital, Richmond Hill, Ont.

Case no.	Age, yr	Sex	Patient information	SARS diagnosis	Date of onset of symptoms	Date admitted to hospital	Oxygen required?	Ventilation required?	Outcome as of Apr. 24, 2003
1	77	M	Index patient	Probable	Mar. 12	Mar. 14*	Yes	Yes	Dead
2	77	F	Spouse of index patient	Probable	Mar. 18	Mar. 21	Yes	Yes	Alive, in hospital
3	43	F	Dialysis nurse for index patient	Probable	Mar. 21	Mar. 29	No	No	Alive, discharged
4	75	F	ICU patient in bed adjacent to index patient	Probable	Mar. 23	Mar. 14*	Yes	Yes	Dead†
5	59	F	ICU nurse caring for index patient	Probable	Mar. 23	Mar. 27	No	No	Alive, discharged
6	47	F	Visitor in same CCU as index patient at referring hospital on Mar. 15	Probable	Mar. 24	Mar. 27	Yes	Yes	Alive, discharged
7	27	F	ICU nurse caring for index patient	Probable	Mar. 25	Mar. 28	Yes	No	Alive, discharged
8	24	F	Ward nurse caring for patient 2	Probable	Mar. 27	Apr. 1	Unknown	No	Alive, discharged
9	29	F	Ward nurse caring for patient 2	Probable	Mar. 28	Apr. 1	Yes	No	Alive, discharged
10	49	F	Nursing assistant caring for patient 2	Probable	Mar. 28	Mar. 28	Yes	No	Alive, discharged
11	44	F	ICU physiotherapist for index patient	Suspect	Mar. 31	Apr. 1	No	No	Alive, discharged
12	61	M	Porter, transported patient 2	Probable	Mar. 31	Apr. 5	Yes	No	Alive, discharged
13	48	F	Hospital administrator‡	Probable	Mar. 31	Not admitted	No	No	Alive
14	80	F	Patient sharing semi-private room with patient 2	Probable	Apr. 1	Feb. 8*	Yes	No	Dead†
15	80	M	Patient in ICU 3 beds away from index patient	Probable	Apr. 2	Mar. 27*	Yes	Yes	Alive, in hospital
16	38	M	Ward nurse on same floor as patient 2	Probable	Apr. 4	Apr. 6	No	No	Alive, discharged

Note: SARS = severe acute respiratory syndrome, ICU = intensive care unit, CCU = cardiac care unit.
*Nosocomial transmission in a patient who was already admitted or had previously been admitted to hospital.
†Death occurred after patient had been transferred to another health care facility.
‡No identifiable close contact (defined as someone "having cared for, lived with, or had direct contact with respiratory secretions or bodily fluids of a suspect or probable case of SARS"[6]).

the hospital-wide implementation of respiratory isolation and barrier precautions. It is also possible that some visitors to the hospital may not have been made aware of the risk of potential SARS exposure and quarantine instructions, despite the high media profile given to this outbreak. These individuals would also be at a much lower risk of contracting SARS due to the lack of opportunity for close contact with a symptomatic patient. Our precision at diagnosing infection caused by the SARS coronavirus is limited by the current epidemiologically based definition. It is possible that some of the current staff and patients diagnosed with probable or suspect SARS were not actually infected by the SARS coronavirus, because many of the clinical features of SARS are shared by a variety of common nosocomial infections, as well as community-acquired respiratory infections. As the identification of an epidemiological link becomes more difficult through successive generations of transmission, our ability to accurately distinguish SARS from other illnesses is impaired. This highlights the urgent need for a rapid laboratory test to identify illness caused by the SARS coronavirus.

In this study, we illustrate how the rigorous application of respiratory isolation and barrier precautions is an effective means of controlling the spread of this disease in the hospital setting. Hospital workers remain on the front lines in the global response to SARS. They are at considerable risk of contracting SARS when there is an opportunity for unprotected exposure.[4,8,11] Continued vigilance is required in the screening of hospital staff, patients and visitors to prevent the future introduction of this disease into hospitals. Public health efforts focused on identifying the close contacts of new patients should help to limit the spread of SARS from the hospital setting to the community. Further study of the utility of mass voluntary quarantine measures in the management of future SARS outbreaks is warranted.

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Competing interests: None declared.

Contributors: Dr. Dwosh was the principal investigator and initiated and developed the study thesis and design. He collected and reviewed clinical data and drafted and edited the manuscript. Dr. Hong provided clinical data, contributed substantially to the study design and framework, and critically revised the manuscript. Dr. Austgarden provided clinical data and a critical review of the manuscript. He prepared the background literature review. Dr. Herman provided clinical data and a critical review of the manuscript. Dr. Schabas contributed to conception of the study, critical review and revision of the manuscript. All authors approved the final version.

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Case report

Enteroviruses and sudden deafness

Ami Schattner, Doron Halperin, Dana Wolf, Oren Zimhony

Abstract

A YOUNG, HEALTHY MAN PRESENTED with sudden severe sensorineural hearing loss and tinnitus. The results of the workup and neuroimaging were normal, as were the auditory brain stem responses. Methylprednisolone pulse therapy was associated with significant hearing improvement within 10 days. A history of a short self-limited febrile illness preceding admission (with headache, photophobia, myalgia and fatigue), a raised serum C-reactive protein level and transient leukopenia suggested an infectious cause. Lumbar puncture revealed a mononuclear pleocytosis of the cerebrospinal fluid, with negative cultures but positive polymerase chain reaction test results for enterovirus, which was later cultured from the patient's stool. The patient's wife and baby had had a similar febrile illness without hearing loss 10 days earlier, and an outbreak of enterovirus meningitis was identified in the area, which was associated with familial clustering and echovirus serotype 4 infection. The varied causes of sudden sensorineural hearing loss, which should include enterovirus, are reviewed here.

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Case

A healthy 27-year-old man was admitted to hospital in Israel in October 2001 with sudden severe bilateral hearing loss. Four days earlier, he had developed fatigue, myalgia and headache and then had a fever (38.5°C) over 1 day and had vomited once. His headache had intensified over the previous 2 days and was associated with photophobia. On the day of admission, he noted the sudden appearance of bilateral tinnitus and hearing loss. On examination, the patient was afebrile and had no signs of meningeal irritation or neurological deficits other than severe bilateral sensorineural hearing loss (SNHL).

The results of complete physical, neurological and ophthalmological examination were otherwise normal. The ECG, chest radiograph and laboratory studies were notable only for a serum C-reactive protein level of 0.36 (normally < 0.08) g/L, serum fibrinogen 4.85 (normally < 4.00) g/L and mild leukopenia (leukocytes 4.1 [normally 5.0–10.0] $\times 10^9$/L), which later became normal. The initial investigation was directed mainly at varied infectious causes, hematological malignancies and autoimmune diseases. Serological tests for herpesviruses, hepatitis viruses, HIV and influenza viruses, as well as for syphilis, Lyme disease, mycoplasma, chlamydia and rickettsiae, were negative on admission and during convalescence. No autoantibodies were found.

Pure tone audiometry showed an average speech reception threshold (the mean of the thresholds at the frequencies of 0.5, 1 and 2 kHz) of 60 dB in the right ear and 65 dB in the left ear, with a 76% discrimination score, which measures ability to discriminate speech on speech audiometry. All measured frequencies, from 250 to 8000 Hz, were affected (Fig. 1). Auditory brain stem responses showed normal peak and interpeak latencies on both sides.

The results of brain imaging (CT with contrast and MRI with gadolinium) were normal.[1] A lumbar puncture was performed to look for "aseptic" meningitis and study cerebrospinal fluid (CSF) cell cytology and oligoclonal IgG.[2] It revealed CSF under normal pressure, with normal protein and glucose levels and 0.11 $\times 10^9$/L leukocytes (97% mononuclear cells) of normal morphology on cytological examination. The findings of microbiological stains and cultures were negative.

The patient was treated with methylprednisolone pulse

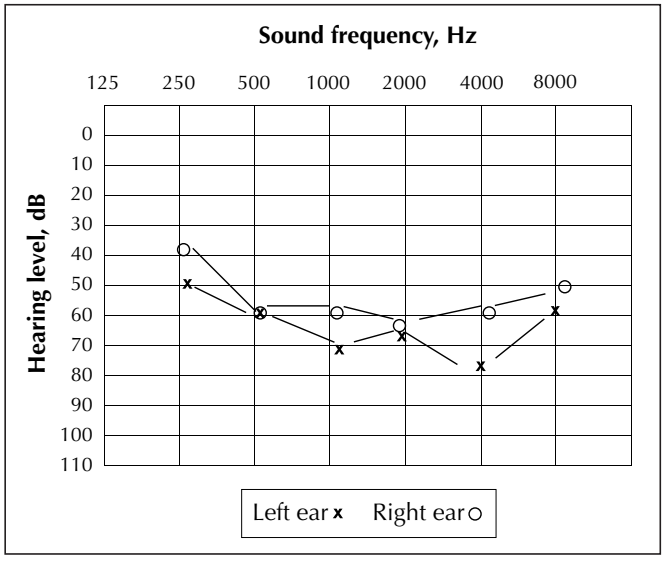

Fig. 1: Results of pure tone audiometry carried out on the patient's presentation.

therapy (1 g/d intravenously, over 3 days) followed by prednisone, 60 mg/d, which was gradually tapered off. He continued to complain of persistent tinnitus and hearing loss. On the fifth day in hospital, an objective improvement in hearing was first demonstrated, and at 10 days a dramatic improvement was found, with speech reception thresholds of 15 dB (right ear) and 25 dB (left ear) at all measured frequencies and 100% discrimination.

The patient then recalled that his wife and baby daughter had had a short self-limited illness about 10 days before his admission: both had fever, vomiting and diarrhea, which resolved spontaneously within 2–3 days. In addition, epidemiological data indicated that over the 8–10 weeks preceding admission an outbreak of enterovirus infections was documented in Israel. The patients, mostly children and young adults, were admitted to hospital with aseptic meningitis. The virus in this outbreak had been cultured and identified as an echovirus of the same serotype (echovirus type 4). On several occasions familial clustering was observed, explained by the known spread of enterovirus from person to person via the fecal–oral route.[3]

The patient's CSF, which had been kept frozen, was therefore re-examined: following extraction, the RNA was subjected to reverse transcription polymerase chain reaction (PCR) using enterovirus universal primers in one reaction tube, as described elsewhere.[4] The sample was tested along with positive and negative buffer and CSF controls, taking special precautions to avoid contamination. The amplification product was detected on microwell plates containing an immobilized oligonucleotide probe specific for enteroviruses (Chemicon International Inc., Temecula, Calif.), using enzyme immunoassay. PCR revealed clear evidence of enterovirus infection. The virus was later cultured from the patient's stool.

Box 1: Main causes of sudden sensorineural hearing loss (SNHL)*

Infections
Viral cochleitis associated with herpesviruses, parainfluenza virus, influenza, mumps, measles, rubella or HIV; bacterial meningitis; *Mycoplasma pneumoniae* infection; Lyme disease; tuberculosis, syphilis or fungal infection

Ototoxic drugs
Aminoglycosides, vancomycin, erythromycin, loop diuretics, antimalarials, cisplatin

Neoplasms
Acoustic neurinoma; meningeal carcinomatosis; lymphoma, leukemia or plasma cell dyscrasia

Trauma
Head injury; barotraumas; noise exposure

Autoimmune diseases
Autoimmune inner ear disease; Cogan's syndrome; Susac syndrome; systemic lupus erythematosus; antiphospholipid antibody syndrome; rheumatoid arthritis; Sjögren's syndrome; relapsing polychondritis; vasculitides (polyarteritis nodosa, Behçet's disease, Kawasaki disease, Wegener's granulomatosis, temporal arteritis or primary central nervous system vasculitis)

Vascular disorders
Vertebrobasilar cerebrovascular accident or transient ischemic attack; cerebellar infarction; inner ear hemorrhage

Varied causes
Meniere's disease; otosclerosis; Paget's disease; multiple sclerosis; sarcoidosis; hypothyroidism; idiopathic SNHL

*In many of the conditions listed, SNHL can be the presenting manifestation of the disease. Sometimes, both ears may be affected simultaneously.

Comments

We report the case of a young man who presented in the fall with self-limited aseptic meningitis and sudden severe bilateral SNHL caused by enterovirus infection. The diagnosis was established by PCR and supported by epidemiological and microbiological data.

Sudden SNHL is defined as hearing loss of 30 dB or more over at least 3 contiguous audiometric frequencies occurring within hours to less than 3 days.[5,6] This is often an alarming experience for the patient, particularly when both ears are affected simultaneously, which is an uncommon occurrence. For the clinician, it constitutes a considerable diagnostic challenge, because it may be caused by many diverse conditions, which may be difficult to recognize, especially when sudden SNHL is the presenting manifestation (Box 1).[5–12] Enteroviruses have not been previously associated with SNHL.

Many cases of SNHL elude definitive diagnosis.[13] Nevertheless, patients can often be offered specific therapy, provided a timely diagnosis can be made.[5,14] Enterovirus infections are quite common, especially in the summer and fall, but often remain undetected.[3] Our findings suggest that the availability of the highly sensitive PCR test for enterovirus allows better understanding of the full scope of enterovirus-associated neurological manifestations. The possibility that enterovirus infections may be associated not only with aseptic meningitis but also with viral cochleitis and sudden SNHL should be recognized. It may even account for some hitherto "idiopathic" cases of SNHL. The recent development of pleconaril, which may be used as specific therapy for enterovirus infections,[14,15] highlights the importance of early diagnosis of enteroviruses as the cause of otherwise idiopathic sudden hearing loss.

This article has been peer reviewed.

From the Hebrew University and Hadassah Medical School (all authors) and the Hadassah University Hospital (Wolf), Jerusalem, and the Kaplan Medical Center, Rehovot (Schattner, Halperin and Zimhony), Israel.

Competing interests: None declared.

Contributors: Drs. Schattner, Halperin and Zimhony diagnosed the case and treated the patient. Dr. Wolf performed the PCR testing and monitored the enterovirus outbreak. Dr. Schattner drafted the article, and all authors participated in its preparation and revision.

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Pesticide use for West Nile virus

Howard Shapiro, Sandra Micucci

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West Nile virus (WNV) caused an unprecedented amount of arthropod-borne illness in Canada in 2002. Since then, we have been working on approaches to mosquito control: one of us (H.S.) has been involved in a cooperative group of southern Ontario public health departments to work through some of the issues in implementing mosquito control measures (the Central East West Nile Virus Work Group), and the other (S.M.) has been researching the effectiveness of pesticides in preventing the spread of WNV (Public Health Research, Education and Development Program, City of Hamilton). In this article, we comment on the general approach to WNV being taken by a number of public health units in southern Ontario.

The prevention of human illness from WNV involves far more than truck-mounted spraying of pesticides. A full response to WNV comprises 3 main components: public education, surveillance and mosquito control. At a local level these components need to be coordinated with elected officials, various city departments (roads, parks, public works, animal services, by-law and communications), conservation authorities, provincial and federal ministries of health, and regulatory agencies.

Public education is essential to help people understand WNV, to encourage people to eliminate mosquito breeding sites on their own property and to promote personal protective measures to avoid mosquito bites. Unfortunately, it is difficult to change personal behaviours, and thus the efficacy of personal protective measures will be limited.[1] Education also plays a key role in helping people to understand what mosquito control is, how it works, why it is important and its potential health and environmental impacts.

Surveillance of bird deaths (e.g., of Corvidae birds such as crows and jays), adult mosquitoes, mosquito breeding sites and human cases of WNV will provide an indication of the extent and location of WNV activity throughout the season. This information will help guide local decisions to intensify activities during the WNV season, such as issuing an alert or increasing mosquito control in an area of high risk. In addition, surveillance data collected over a number of years will help to refine control strategies further.

The last component in the prevention of human WNV infection is mosquito control. Knowledge of mosquito biology and local conditions should be used to choose the best interventions (habitat modification, water management, sanitation or pesticides) on a site-specific basis.

The control measure that raises most public concern is pesticide use. Pesticides are designed to act at 2 of the stages in the mosquito life cycle (Fig. 1). Immature mosquitoes develop from eggs to larvae to pupae in standing water, and pupae develop into winged adults. Agents that work in standing water against mosquito larvae are termed larvicides, and those that work against winged mosquitoes are termed adulticides.

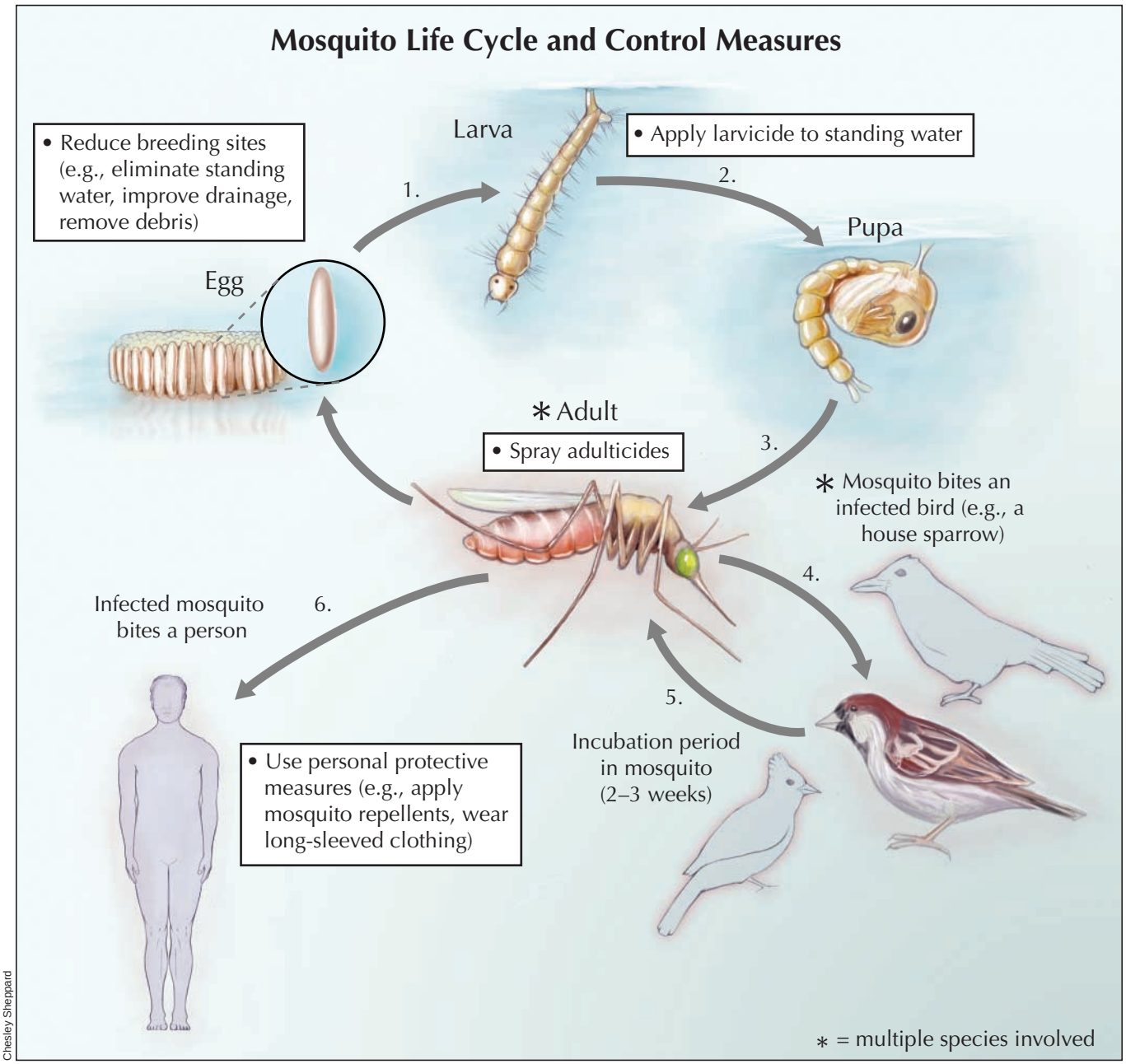
Larvicides have a number of advantages over adulticides. Their use can be targeted to mosquito breeding sites, which avoids a wide application over an entire neighbourhood or city. They can be applied in solid form (e.g., pellets, granules and sand), which limits human exposure. Some larvicide agents are specific to mosquitoes when used according to directions and have relatively little impact on the environment and human health. Formulations are available that can prevent the emergence of adult mosquitoes for up to 1 month, which decreases labour costs.

Adulticides are most often applied as a very fine ultra-low-volume (ULV) droplet spray from a truck or aircraft. Adulticide operations dominate media coverage of WNV control, although they are only one part of control efforts. Adulticides applied as a ULV spray work by coming into direct contact with adult mosquitoes as they are flying. One criticism of adulticides is their transient effect: mosquito numbers return to pretreatment levels within a few days without repeat applications. The use of adulticides in many jurisdictions is reserved for response to human cases of WNV infection or environmental findings (WNV-positive birds or mosquitoes) that indicate a high level of human risk of WNV infection from adult mosquitoes.[2,3]

Every pesticide in Canada has to pass a science-based assessment by Health Canada's Pest Management Regulatory Agency (PMRA). The agency takes this information into account and provides reassurance as to the safety and potential usefulness of the pesticides when used as directed. However, critics of pesticide use have expressed concerns about their effectiveness and their impact on human health and the environment.

The effectiveness of pesticides for mosquito control has been reported in many different ways, from controlled ex-

periments in a laboratory setting[4] to descriptive reports of mosquito control programs over a wide geographic area.[5] That pesticides kill mosquitoes (with varying levels of effectiveness depending on the product and species) when applied as larvicides to small, well-defined locations (e.g., ponds, catch basins, wetland areas) is supported by findings from controlled studies.[6,7] Reports of before–after studies also provide evidence that mosquito control efforts lower the numbers of mosquitoes in a given neighbourhood or city.[8] Unfortunately, randomized controlled trials of the effectiveness of mosquito control using human arboviral disease as an end point are not possible for practical reasons



Chesley Sheppard

Fig. 1: Schematic of the mosquito life cycle and control measures. The development of immature mosquitoes from eggs to larvae to pupae occurs in standing water. These stages of the mosquito life cycle can be disrupted by eliminating standing water where possible and by applying larvicides to water bodies containing larvae. When the pupae develop into winged adults, mosquitoes acquire West Nile virus by biting infected birds. The incubation period in mosquitoes is about 2–3 weeks. An infected mosquito might then bite a person, passing the virus on. Many bird species act as reservoirs for the virus, and many mosquito species are involved in passing the infection from bird to bird, or from bird to human, or both. Populations of adult mosquitoes can be controlled by spraying adulticides. Individuals can reduce their exposure to mosquitoes by undertaking personal protective measures.

(e.g., the wide variety of local environmental conditions, the variety of mosquito species and the usually small numbers of human cases). This lack of evidence, especially as it concerns mitigation of human disease, is echoed by many experts.[9,10] Nonetheless, mosquito control, especially the use of larvicides, is a recommended response to WNV by the US Centers for Disease Control and Prevention.[2] Draft guidelines from Health Canada make similar recommendations but are not yet publicly available (Dr. Robbin Lindsay, National Microbiology Laboratory, Winnipeg: personal communication, 2003).

The 2 larvicides being considered by most public health units in Canada — methoprene and *Bacillus thuringiensis* subsp *israelensis* (commonly referred to as Bti) — have been used for many years and have well-documented track records of human and environmental safety.[11–13] Both of these larvicides pose little risk to human health either through direct handling of the products or indirect exposure to them as a result of their use for mosquito control. Mild skin and eye irritation have been reported from direct contact with Bti.[12]

Methoprene has been shown to be toxic to some insects closely related to the mosquito, has very low toxicity to mammals, is moderately toxic to warm-water and freshwater fish, is slightly toxic to cold-water fish and is acutely toxic to some estuarine invertebrates.[13] Toxicity of methoprene to insects and animals other than mosquitoes and blackflies occurs at concentrations much higher than those used for mosquito control.[13] Bti is toxic to a lesser range of species than methoprene but is also effective against a lesser range of mosquito species.[12] Both larvicides break down rapidly in the environment.

Unlike the application of larvicides, which is in standing water usually remote from people and is limited in scope, adulticides must be applied widely in the air, which puts other insects, birds, fish, crustaceans and mammals, including people, at increased risk of exposure to them.

Malathion is the main adulticide being considered for mosquito control in Ontario. Many of the products used for mosquito control in the United States (e.g., synergized pyrethroids such as sumithrin and piperonyl butoxide) are not available for use in Canada. Malathion is an organophosphate pesticide that has been used in Canada since 1953. In addition to its use for mosquito control, it has registered residential uses for insects on lawns, gardens and ornamental trees, shrubs and plants in Canada and the United States. An extensive re-evaluation of malathion was completed by the US Environmental Protection Agency in 2000.[14] The PMRA has also re-evaluated malathion and approved its use as a mosquito adulticide.[15] Among the available agents used for mosquito control, malathion has the most current and comprehensive safety information available. It works by inhibiting cholinesterase and is detoxified by carboxylesterases into polar, water-soluble compounds that are then excreted.[16] Mammals have greater carboxylesterase activity than insects, which accounts for the selective toxicity of malathion toward insects. Cholinesterase inhibition in humans can overstimulate the nervous system and result in nausea, dizziness, confusion and, at very high exposures (e.g., accidents, major spills), respiratory paralysis and death.

A comprehensive literature review, risk assessment, and epidemiologic and attributable risk analyses of adulticides, including malathion, were performed by the Westchester County Board of Health, New York.[11] The board concluded that no significant adverse human health effects would be expected from adulticides used in accordance with its mosquito control plan. It concluded that the active ingredients in the adulticides may cause short-term effects, such as skin irritation or respiratory effects for some sensitive individuals, but were not expected to increase asthma events or other respiratory effects significantly. Similar conclusions have been reached by the US Environmental Protection Agency[14] and the PMRA.[15]

Malathion has low toxicity to birds and mammals and is not expected to pose a hazard to them.[14] It degrades rapidly in the environment, especially in moist soils. But there are some environmental concerns with malathion. It is highly toxic to insects and to aquatic organisms, including fish. The toxic effects on aquatic organisms can be decreased by limiting drift of the adulticide around water.

That pesticides kill mosquitoes when used as directed is not much in doubt. The issue is whether mosquito numbers can be lowered enough to have a significant impact on human illness from WNV. In trying to prevent WNV infection, public health units face a challenge of balancing the risk of infection against the risk of human and environmental exposure to the pesticides used for mosquito control. Given some of the uncertainties surrounding WNV, owing to the recent arrival of the virus in North America and the newness of resulting mosquito control programs, it would be scientifically responsible to ensure that WNV control programs are evaluated using appropriate methods and the findings disseminated to the community.

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Excluding pulmonary embolism with helical (spiral) computed tomography: Evidence is catching up with enthusiasm

Clive Kearon

Advances in computed tomography (CT) technology have enabled imaging of the pulmonary arteries with injection of contrast medium into an arm vein. This technique, which involves continuous imaging with a rotating gantry as the patient is moved through the scanner, is usually referred to as "helical," "spiral" or "continuous-volume" CT, and it is now widely used to diagnose pulmonary embolism. Enthusiasts have proposed that helical CT is accurate enough to "rule in" or "rule out" pulmonary embolism in most patients. These claims have been based on the results of mostly small studies that reported high accuracy of helical CT in the diagnosis of pulmonary embolism when compared with an established diagnostic standard, usually ventilation–perfusion lung scanning and conventional pulmonary angiography. However, until recently, the methodologic limitations of studies evaluating helical CT in the diagnosis of pulmonary embolism have cast doubt on this technique's accuracy and led to uncertainty as to how helical CT should be used in clinical practice.[1,2]

Using the estimated accuracy of helical CT and extrapolations from experience with ventilation–perfusion scanning, I recently recommended in *CMAJ* how helical CT should be used to diagnose pulmonary embolism.[3] The results of 2 recent, well-designed studies of helical CT in the management of patients with suspected pulmonary embolism[4,5] strengthen those recommendations and allow the role of helical CT for the exclusion of pulmonary embolism to be extended. These studies tested the safety of withholding anticoagulant therapy on the basis of negative results of both helical CT for embolism and ultrasound examinations of the legs for proximal deep-vein thrombosis. Single-detector helical CT scanners, rather than more modern multidetector scanners that have better spatial resolution, were used in both studies.

In France, Musset and colleagues[4] performed a standardized clinical assessment of pulmonary embolism probability, helical CT of the pulmonary arteries and bilateral ultrasonography of the proximal deep veins of the legs (including the calf-vein trifurcations) in 1041 patients with suspected pulmonary embolism. Anticoagulant therapy was withheld from 507 patients on the basis of a combination of low or moderate clinical probability of pulmonary embolism and negative results of both helical CT and ultra-

sonography; during 3 months of follow-up, venous thromboembolism developed in 9 patients (1.8%; 95% confidence interval [CI] 0.8%–3.3%).

In the Netherlands, van Strijen and associates[5] performed helical CT in 510 patients with suspected pulmonary embolism. If the results were negative for pulmonary embolism and did not reveal a clear alternative diagnosis, ultrasonography of the proximal veins of the legs was performed. If those results were normal, ultrasonography was repeated after 4 and 7 days. Of the 130 patients in whom helical CT revealed an alternative diagnosis, 2 (1.5%, 95% CI 0.2%–5.6%) had venous thromboembolism during 3 months of follow-up. Of the 246 patients in whom ultrasonography was repeated, none had ultrasonographic abnormalities on day 4 or 7, and only 1 patient (0.4%, 95% CI 0.0%–2.2%) had venous thromboembolism during 3 months of follow-up.

On the basis of the findings in these 2 studies, I believe that it is safe to consider pulmonary embolism excluded if the results of helical CT of the pulmonary arteries and ultrasonography of the proximal deep veins of the legs are negative for embolism and thrombosis, respectively, provided the clinical probability of embolism is low or moderate. Because pulmonary embolism was found in 5% of the patients who had a high clinical probability but negative results of both helical CT and ultrasonography,[4] I recommend further testing for such patients.[3] It is important to note that negative results of helical CT alone do not exclude pulmonary embolism in patients with a low or moderate clinical probability; ultrasonography should also be performed to look for proximal deep-vein thrombosis in the legs. If helical CT reveals a clear alternative diagnosis, it may be safe to exclude pulmonary embolism without ultrasonography; however, in my opinion, there is still insufficient evidence to support such a recommendation.

Major advantages of helical CT over ventilation–perfusion scanning are that fewer examinations — 10%(4,5) v. 60%(3) — are technically inadequate or "nondiagnostic" and that helical CT identifies an alternative diagnosis that may influence clinical management in about 25% of patients.[5] The main disadvantage of helical CT is that, unlike ventilation–perfusion scanning, a negative result does not exclude pulmonary embolism.[1–4] However, the new French and Dutch studies indicate that ultrasonography of the proximal deep veins of the legs in patients with helical CT scans negative for pulmonary embolism overcomes this limitation in most patients.

Although the French study found that helical CT abnormalities confined to subsegmental pulmonary arteries were nondiagnostic, neither study systematically tested the positive predictive value for pulmonary embolism of helical CT abnormalities or of abnormal ultrasound examinations when combined with negative helical CT scans. The Second Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED 2) is evaluating the accuracy of helical CT and ancillary investigations in the diagnosis of pulmonary embolism in more than 1000 patients. This study, funded by the US National Institutes of Health, should bring us closer to an answer to these questions.

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SARS: prudence, not panic

Richard Schabas

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ß See related articles pages 1415 and 1434

As I write this article (on Apr. 21, 2003), Ontario is well into the eighth week of an outbreak of severe acute respiratory syndrome (SARS). SARS is an important new respiratory infection capable of causing significant levels of illness and death, particularly in compromised patients. To date, 128 Ontarians have met the case definition for probable SARS,[1] and 13 of these have died.[2]

Ontario, where most of Canada's 132 cases of SARS and all of its SARS-related deaths have occurred, has declared a health emergency to deal with the disease and has used aggressive measures to try to control it.[3] Hospital services have been drastically curtailed. Two hospitals have been closed outright. Thousands and thousands of people (including me) have been quarantined.

Despite these efforts, there has been a slow but steady flow of new infections from community settings. The Toronto media[4,5] and some physicians (A. Detsky and T. Stewart, Mount Sinai Hospital, Toronto: personal communication, Apr. 17, 2003) are calling for even more aggressive measures to stamp out SARS. Public health officials are reportedly considering "worst case" scenarios.[6]

Now is a good time to pause and take stock. Our experience with SARS in Canada is now less than 2 months old, but our knowledge has grown substantially. Our understanding of SARS today is very different from what it was even 2 weeks ago, and it may be very different 2 weeks from now. We need to assess what we have learned and apply this knowledge. Certainly SARS is a serious problem that needs to be dealt with seriously. Yet our actions must be based on facts and experience, not on fears. The response should not be worse than the disease.

Let's look at the good news about SARS. First, it might help to put SARS in perspective. In the 8-week period since SARS hit Ontario, the province could expect to see about 100 deaths from influenza (Teresa Tam, Health Canada, Ottawa: personal communication, Apr. 21, 2003), 200 deaths from motor vehicle crashes[7] and 2000 deaths from tobacco addiction.[7]

Second, transmission of SARS appears to be by respiratory droplets, not airborne spread.[8] Hence, SARS does not appear to be highly infectious for casual contacts.[9] Other routes of transmission (e.g., sewage contamination) may be plausible but do not appear to be playing a role in Canada.[10]

Third, SARS is not behaving like the next great pandemic. SARS has been present in Guangdong province in China since November 2002. Even if we allow for underreporting, we are still counting cases worldwide in the thousands, not the millions.[11] If SARS behaved like pandemic influenza, the case count would now be much, much higher.

Fourth, nosocomial spread, which played a critical role in the first phase of the Ontario outbreak, has been effectively curtailed. The hospital system responded, and the respiratory precautions have worked very well. My own hospital, York Central, had 15 cases of nosocomial SARS caused by infection acquired in the 12 days between March 16 and March 28. However, there have been no cases of SARS transmission in the subsequent 3 weeks, following the introduction of stricter respiratory precautions.[12] Breakdowns in the precautions will occur, but overall the benefits have been impressive.

Fifth, we are rapidly developing experience in treating SARS. Clinicians are communicating with each other and publishing their experiences in real time.

Sixth, the virus that causes SARS has already been identified,[13] and accurate diagnostic tests will probably be available soon.

The bad news, of course, is that SARS is now established in Ontario and is spreading in the community, in Toronto and elsewhere in Canada. Suspect cases have been reported in at least 6 Canadian provinces.[14] These developments should not come as a surprise. SARS was present in the community from the beginning. The first few cases in Ontario were community-acquired, although they were soon overshadowed by nosocomial cases.[9]

Ontario's response to SARS has been energetic. Unfortunately, however, it appears to have been based on unachievable expectations, specifically, that quarantine would eliminate the disease. Let's be realistic. Quarantine plays an important but limited role in the community control of respiratory infections. It can reduce the impact of an outbreak but, according to our experience with other respiratory diseases, it won't stop transmission entirely.

The future of SARS is uncertain. A number of scenarios are plausible. The disease may yet develop into a major pandemic, with explosive growth in the number of cases, but I consider this very unlikely given the behaviour of the outbreak to date. At the opposite extreme, SARS may dis-

appear as mysteriously as it appeared. This could happen if SARS is insufficiently infectious to sustain transmission in our social environment. As an incorrigible optimist, I actually regard this as the most likely course of events, in Canada at least. The epidemic curves of SARS in Canada and elsewhere lend credence to this view.[15]

We should not, however, base our current planning on either of these extreme-case scenarios. Our planning for SARS should be based on an in-between scenario. We will continue to see new SARS cases, usually at relatively low levels but with occasional flare-ups. In other words, we should plan on getting used to living with SARS. SARS will be a problem everywhere, not just in Toronto, Hong Kong and Singapore. We can anticipate spread from community to community and, sporadically, by international travellers. Our SARS control strategy must therefore be global.

Under this scenario, what should we do? We need realistic goals and sustainable interventions. I have several recommendations.

First, we must tighten our control of respiratory infections in acute care hospitals. This is the single most important measure and one that we now know can be effective. Until we have a rapid and accurate diagnostic test for SARS, all patients with pneumonia admitted to hospital in areas where SARS is active must be treated under full respiratory precautions: N95-rated mask (95% filtration efficiency against solid and liquid aerosols), gown, gloves and eye protection. This approach will place severe strain on our already stretched acute care hospitals. But it is the new reality that York Central and other Toronto area hospitals, as well as hospitals in Hong Kong, Singapore and parts of China, are already facing. Good respiratory precautions and routine screening of staff and visitors for fever and respiratory symptoms should be sustainable in a fully functioning hospital. Cancellation of elective hospital services is unsustainable and probably unnecessary.

Second, public health should get back to basics. Mass quarantine of casual contacts has sapped public health resources and contributed very little to SARS control. Instead, the public health sector should focus its efforts on general surveillance of respiratory illnesses, SARS case finding and investigation, isolation of close contacts of SARS cases, and public and professional education. These activities are consistent with the recommendations of the World Health Organization.[16]

Third, there is an urgent need to develop and implement strategies for managing SARS-like illness in community health care settings. The offices of family doctors are rapidly becoming the front lines in the battle against SARS, and there have already been several cases of SARS in family doctors.[17] Community health care providers need to be ready to don masks, gloves and goggles when they see patients with a respiratory illness. This will pose logistical challenges for family doctors. Practical protocols are required now.

Fourth, clinicians need to collaborate to generate an evidentiary — or at least an experiential — basis for the treatment of SARS. For example, many clinicians treating SARS in Toronto started by using ribavirin because they thought that it was the standard. They discovered, through a regular teleconference, that none of them believed that it was actually helpful, and their practices changed accordingly (T. Stewart, Mount Sinai Hospital, Toronto, personal communication: Apr. 17, 2003). Sharing experiences and opinions is very helpful. Medical journals are contributing by fast-tracking articles and publishing them on the Internet.

Finally, we need to get on with our lives. Poor communication, excessive precautions and failure to meet unrealistic goals have fuelled public fears. The social, economic and health costs have been substantial. Even more draconian measures, unwisely advocated by some Toronto newspaper editorials,[4,5] would be ineffective and would cause much further harm.

Good decision-making in a crisis is always difficult. It depends on our learning from experience and adjusting our response to fit the circumstances. Public health officials must show leadership in restoring calm and balance to the battle against SARS. Regaining public confidence is a priority.

Editor's note: The personal communication cited in the third paragraph from the end of this article has been amended since online publication.

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Competing interests: None declared.

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Why was Toronto included in the World Health Organization's SARS-related travel advisory?

Guénaël R.M. Rodier

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ß See related articles pages 1415 and 1432.

On Apr. 23, the World Health Organization (WHO) advised international travellers to consider postponing all but essential travel to Beijing and Shanxi Province, China, and to Toronto. This advice was based on an assessment of the risk that travellers to these 3 areas might become infected with the SARS virus during their stay and export the disease to another country, possibly seeding an outbreak there. Similar advice to travellers contemplating visits to Hong Kong and Guangdong Province, China, had been issued Apr. 2.

Factors considered when making these assessments include the magnitude and dynamics of the outbreak measured, in part, through data on the prevalence of cases (total number of reported cases minus patients who have recovered or died) and the number of new cases detected each day. Another key factor is the occurrence of local chains of transmission outside a confined setting, such as a health care environment. When an outbreak is large and dynamically evolving, the likelihood is greater that time will elapse between the onset of infectivity and the detection and isolation of cases. This lapse, in turn, increases opportunities for further spread within the general community. The risk to international public health occurs when an infected person undertakes international travel, regardless of whether the infection was acquired in the general community or following contact with a high-risk person or in a hospital setting.

SARS is a disease that places extreme demands on hospitals, health care staff and the entire public health system. Experience to date in some of the hardest hit countries indicates that the sheer magnitude of the outbreak can lead to a breakdown in essential public health measures, whether involving infection control in hospitals, contact tracing, quarantine of close contacts, prompt detection and isolation of cases, or exit screening of international travellers. When an infected person is able to board an airplane and undertake international travel, such a breakdown in control measures has clearly taken place.

When issuing the Apr. 23 travel advisory, which included Toronto, WHO epidemiologists considered all of these factors, together with reports of possible cases exported from Toronto, from Mar. 29 through Apr. 3, to Australia, the United States and the Philippines. In the Philippines, which had previously been free of SARS, the presence of a first probable case, epidemiologically linked to a charismatic religious group in Toronto, was reported to WHO Apr. 14. The patient subsequently died, a suspected case in a health care worker has been reported, and numerous contacts are under investigation.

SARS is the first major new infectious disease of the 21st century and, as such, is taking full advantage of the opportunities for rapid international spread afforded by a closely interconnected and highly mobile society. It is the duty of WHO to do everything possible to prevent spread to other countries of a poorly understood, severe disease for which there is no reliable diagnostic test and no effective treatment beyond supportive care. To date, most outbreaks have occurred in countries with good surveillance and strong health care systems. The importation and subsequent spread of SARS in a densely populated country with a poor health infrastructure can have enormous public health consequences, as we are now seeing in parts of China. In all countries with SARS outbreaks, the social and economic consequences have likewise been enormous.

WHO did not make the decision to issue the Apr. 23 travel advisory lightly. In its response to the SARS outbreak, Canada has been a model of transparency in its reporting and public information, of determination in its contact tracing, and of heroic dedication on the part of its medical, health and scientific staff. We are aware of the economic hardship that all travel advisories bring. We are aware, too, that some countries, looking at the example of Toronto, may choose to be less open and frank in their reporting of SARS — or any other epidemic-prone disease with the potential for international spread — for fear of the economic consequences.

We are aware, too, that we have been perceived by some as "punishing" a country that has not only been a model in its efforts to contain a particularly serious SARS outbreak, but has also been one of our strongest and most valued partners in international public health. In the final analysis, however, our decisions must be based first and foremost on public health concerns in the face of a serious health emergency that has amply demonstrated its potential for rapid international spread. Had our international vigilance been in place prior to Mar. 12, Toronto would very likely have been spared a SARS outbreak on the scale it has worked so admirably to contain. All of the most severe SARS outbreaks to date, in Canada, China, Hong Kong, Singapore, and Vietnam, began before health authorities and hospital staff were alert to the rapid spread of a new disease and aware of the need for immediate isolation of suspect cases and strict infection control. The additional 22 countries reporting probable cases to WHO detected their first case after WHO issued its global alert. All but one of these countries have seen very little or no transmission from a few isolated imported cases to others.

On Apr. 29, a day after Vietnam was removed from the list of affected areas, the Director-General of WHO examined data on the status of all countries and areas listed as affected. Although Toronto remains on this list, a decision to lift the travel advisory, effective Apr. 30, was made based on consideration of 3 criteria: a decrease to below the defined threshold level of 60 prevalent SARS cases and 5 new SARS cases per day, a period of 20 days since the last case of community transmission occurred, and no new confirmed cases of exportation. We have also received assurance from health authorities that proactive screening measures at airports will be implemented, as recommended by WHO. Such measures are welcomed at a time in the evolution of a new disease when some hope of containment remains.

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Serotonin syndrome: a brief review

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Case 1

A 50-year-old man was admitted to hospital with hyperhidrosis, nausea, vomiting and diarrhea. He had been taking fluoxetine (120 mg/d), meprobamate (400 mg/d) and acepromazine (13.55 mg/d). The dose of fluoxetine had just been increased. The patient was agitated and had insomnia and hyperreflexia, but there were no focal neurological findings. His blood pressure was 155/80 mm Hg, his heart rate, 96 beats/min, his respiratory rate, 20 breaths/min and his temperature, 37.2°C. The findings of the complete blood count, blood potassium, blood glucose, liver function and kidney function tests, and the erythrocyte sedimentation rate were normal. A blood alcohol test was negative. ECG, chest radiograph, blood gas measurements and a brain CT scan showed no anomaly.

Case 2

A 50-year-old depressed woman was admitted to hospital for agitation, insomnia and tremors. She had been taking citalopram (20 mg/d), prazepam (10 mg/d), meprobamate (400 mg/d) and acepromazine (13.55 mg/d). The patient's blood pressure was 135/70 mm Hg, her heart rate, 130 beats/min, her respiratory rate, 32 breaths/min and body temperature, 37°C. The patient was confused and had hyperhidrosis, hyperreflexia and myoclonus, but there were no focal neurological findings. Her blood electrolytes were normal, her leukocyte count was 13.3 x 10^9/L and her total creatine kinase was 494 U/L (MB isoenzyme fraction < 6%). The aldolase level, liver function tests, and blood creatinine, hemoglobin, platelet and fibrinogen levels were normal. Qualitative plasma tests for alcohol, carbamates, salicylates, paracetamol, barbituates, benzodiazepines and tricyclic antidepressants were negative. ECG indicated sinus tachycardia. The findings of a brain CT scan were normal.

Serotonin (5-HT) is a neurotransmitter with neurons located in the raphe nuclei. Serotonin neurons play a part in sleep–wakefulness cycles, mood, emotional and food behaviours, and thermoregulation.[1] Serotonin syndrome is the result of overstimulation of 5-HT_{1A} receptors (Fig. 1) by selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI) or other serotonergic agents.[2–5] The use of SSRIs is related to the frequency of the syndrome.[2,3] Regardless of age or sex, onset is observed within 24 hours following the administration or overdose of a serotonergic agent.[2,4] Serotonin syndrome is characterized by a triad of mental, autonomic and neurological disorders.[2–4,6–8] Serotonin syndrome is confirmed by the presence of 4 major symptoms or 3 major symptoms plus 2 minor ones.[3,9] Serotonin syndrome can be fatal, but in most cases there is a good prognosis when medication is discontinued.[2,4] Improvement following the administration of cyproheptadine or chlorpromazine has been reported.[3] Further studies of the therapeutic effects of propranolol and ziprasidone, which block 5-HT_{1A} receptors, would be justified.

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Physiopathology

Serotonin syndrome is the result of overstimulation of 5-HT_{1A} receptors in central grey nuclei and the medulla and, perhaps, of overstimulation of 5-HT_2 receptors.[2–4,10] Few cases have been reported in association with citalopram.[2,11] In the case of fluoxetine, a high dose increases the risk of serotonin syndrome.[4,7,9] Drug combinations may also have been involved. Meprobamate, which is metabolized in the liver through hydroxylation and glucuronide conjugation, might slow down the metabolism of a SSRI through competitive inhibition. Promethazine, a competitive inhibitor of 5-HT_2 receptors,[12] might cause hyperactivation of 5-HT_{1A} receptors in the presence of SSRIs.

Several situations indicate an overstimulation of 5-HT_{1A} receptors: excess precursors of serotonin or its agonists and higher release, lower recapture or metabolic slowdown of serotonin (Table 1).[2,3,8] Cases of mild serotonin syndrome have been reported in patients who have taken *Hypericum perforatum* (St. John's wort), an in-vitro 5-HT reuptake inhibitor, in conjunction with SSRIs.[13]

Diagnosis

In order to reach a diagnosis of serotonin syndrome, a history of use of a serotonergic agent, recognized signs and symptoms, and the exclusion of other conditions are required.[2,8,9] Serotonin syndrome involves mental, autonomic and neurological disorders of sudden onset less than 24 hours after the beginning of treatment or an overdose.[2–4,6–9] The diagnosis of serotonin syndrome is guided by the Sternbach criteria[14] but is still difficult in cases of benign symptoms or normal neurological test results.[3,9,15] Radomski and colleagues[9] have revised these criteria and classified serotonin syndrome as a mild state of serotonin-related symptoms, or serotonin syndrome (full-blown form) (4 major symptoms or 3 major ones plus 2 minor ones) (Box 1) or toxic (coma, generalized tonic-clonic seizures, fever that might exceed 40°C).[3,9]

There is no specific test for serotonin syndrome. An elevation of the total creatine kinase and leukocyte count and

elevated transaminase levels or lower bicarbonate levels have been reported.[2,3,8] Disseminated intravascular coagulation, kidney failure, acidosis or acute respiratory distress syndrome are secondary complications.[2,9]

The principal differential diagnosis is neuroleptic malignant syndrome (NMS) (Box 2).[2–4,7,8,10,16] Common criteria are alteration of consciousness, diaphoresis, autonomic instability, hyperthermia and elevated creatine kinase levels. NMS is observed most often following a rapid increase in dosage of a neuroleptic drug.[2,10,17] These symptoms appear within 7 days in 66% of cases.[17] Certain risk factors (dehydration, agitation, organic cerebral disorders) are associated with development of the syndrome following a brief exposure.[18] Our patients were taking a phenothiazine (acepromethazine), one of the antipsychotic drugs associated with NMS, but the absence of hyperthermia and muscular rigidity and the presence of diarrhea and myoclonus were indicators of serotonin syndrome.[19,20] The most frequent differences between serotonin syndrome and NMS are indicated in Table 2.

Treatment

Serotonergic agents must be discontinued.[2,3,9] Monitored intravenous (IV) electrolyte solution is administered in a hospital environment in order to maintain diuresis above

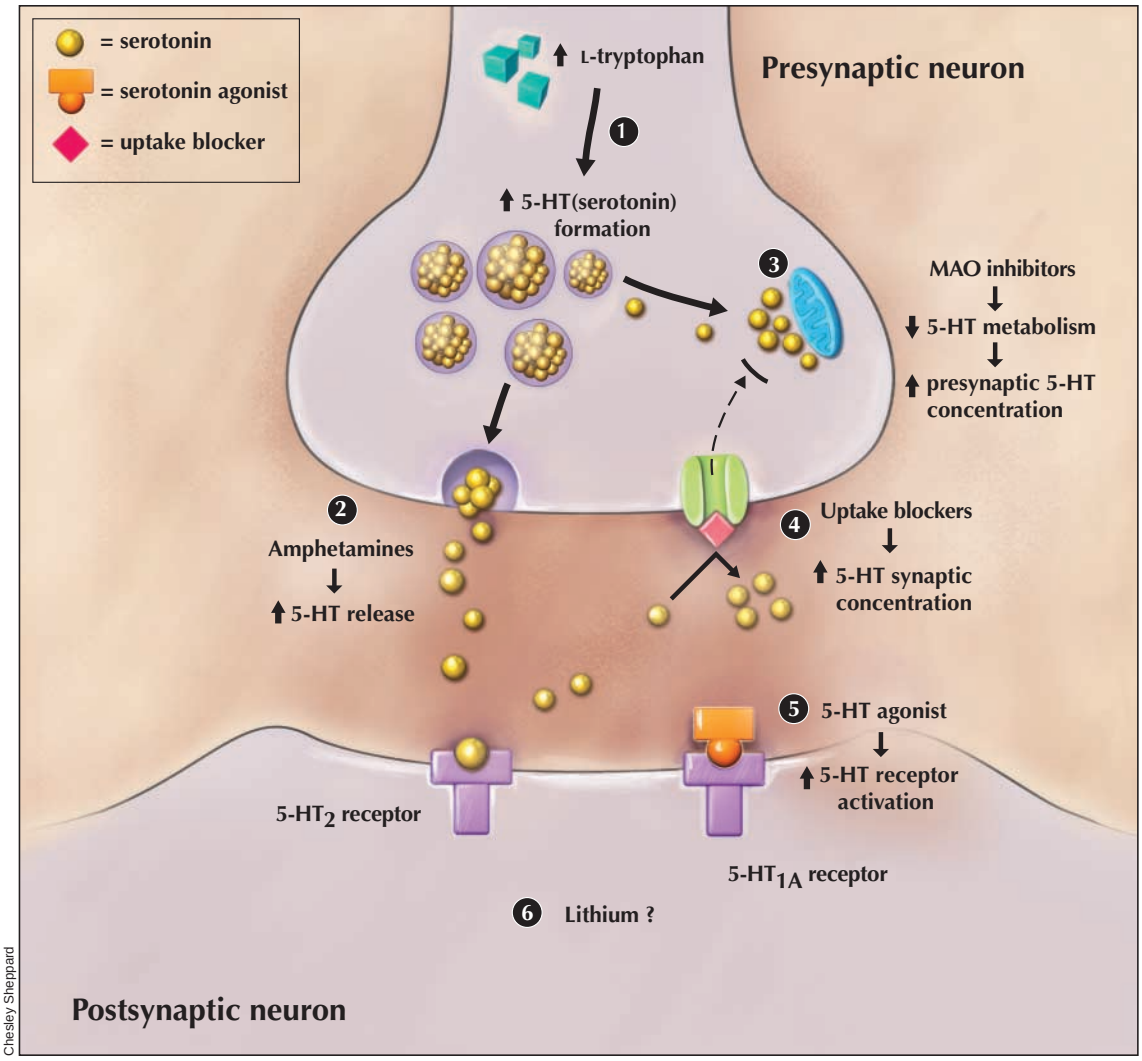

Fig. 1: Mechanisms of serotonin syndrome. (1) Increased doses of L-tryptophan will proportionally increase 5-hydroxytryptamine (5-HT or serotonin) formation. (2) Amphetamines and other drugs increase the release of stored serotonin. (3) Inhibition of serotonin metabolism by monoamine oxidase (MAO) inhibitors will increase presynaptic 5-HT concentration. (4) Impairment of 5-HT transport into the presynaptic neuron by uptake blockers (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants) increases synaptic 5-HT concentration. (5) Direct serotonin agonists can stimulate postsynaptic 5-HT receptors. (6) Lithium increases postsynaptic receptor responses. Adapted with permission from Elsevier Science (*Critical Care Clinics* 1997;13[4]:763-83).

50–100 mL/h and to avoid the risk of myoglobinuria.[3] Benzodiazepines may be prescribed to reduce anxiety. One case of partial improvement has been reported during treatment with propranolol.[21] The benefits of β-blockers, which block 5-HT_{1A} receptors, may be supported by other studies.[16] Resuscitation (cooling off, mechanical ventilation, anticonvulsing agents, antihypertensive agents) may be required for serious cases.[2,3,22,23]

Although their effectiveness has not been demonstrated scientifically, cyproheptadine and chlorpromazine have been described as possible therapy for serotonin syndrome.[2,3] Cyproheptadine is a histamine-1 receptor antagonist with anticholinergic and antiserotonergic characteristics and can cause drowsiness.[22,24] Chlorpromazine is a 5-HT_{1A} and 5-HT_2 receptor antagonist neuroleptic that can have anticholinergic effects and cause hypotension, dystonias or NMS.[3,22,25] Cyproheptadine, which is taken orally, has lesser adverse effects.[3] Among newer antipsychotic drugs, ziprasidone is the most powerful for blocking 5-HT_{1A} receptors.[26] Further study might outline its possible benefits; it has moderate extrapyramidal effects.

Course

Most patients improve completely within 24 hours after being admitted. This is the case for individuals who have been taking cyproheptadine or chlorpromazine.[2] For 40% of patients, some symptoms persist longer. The more powerful the serotonergic agent and the higher the dose, the more serious these symptoms. Duration seems related to the half-life of the drug.[4,27] Prescribing the antiemetic metoclopramide may increase the long half-life of fluoxetines (4–6 days).[28]

Cases revisited

Case 1

A diagnosis of full-blown serotonin syndrome was reached taking into account the sudden increase in dosage of fluoxetine and the presence of 3 major symptoms (elevated mood, hyperhidrosis, hyperreflexia) and 2 minor ones (insomnia, diarrhea). The patient's medication was discontinued. He was administered 3 L of electrolytic solution every 24 hours, 10 mg of IV metoclopramide dihydrochloride every 8 hours and 20 mg of dipotassium clorazepate orally every 12 hours. Nausea, vomiting, diaphoresis and diarrhea disappeared within 72 hours. The patient's anxiety subsided more slowly, and he was discharged 5 days later.

Case 2

A diagnosis of full-blown serotonin syndrome was reached because the patient was taking citalopram, there was probable voluntary overdose and 5 major symptoms (confusion, myoclonus, tremors, hyperreflexia, hyperhidrosis) were present. The medication was discontinued. The patient was administered 3 L of electrolytic solution every 24 hours. The patient's condition improved sufficiently regarding her confusion and the autonomic and neurological symptoms for her to be discharged 24 hours later.

Table 1: Situations that cause overstimulation of serotonin (5-HT_{1A}) receptors[2,3,8]

Situation	Associated drugs
Excess of precursors of serotonin or its agonists	Buspirone, L-dopa, lithium, LSD, L-tryptophan, trazodone
Increased release of serotonin	Amphetamines, cocaine, MDMA ("ecstasy"), fenfluramine, reserpine
Reduced reuptake of serotonin	SSRI, TCA, trazodone, venlafaxine, meperidine
Slowing down of serotonin metabolism	MAOI, e.g., isocarboxazid, selegiline

Note: LSD = lysergic acid diethylamide, MDMA = methylenedioxy-methamphetamine, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, MAOI = monoamine oxidase inhibitors.

Box 1: Revised diagnostic criteria for serotonin syndrome[3,9]*

1. Addition of a serotonergic agent to an already established treatment (or increase in dosage) and manifestation of at least 4 major symptoms or 3 major symptoms plus 2 minor ones

Mental (cognitive and behavioural) symptoms

Major symptoms: confusion, elevated mood, coma or semicoma

Minor symptoms: agitation and nervousness, insomnia

Autonomic symptoms

Major symptoms: fever, hyperhidrosis

Minor symptoms: tachycardia, tachypnea and dyspnea, diarrhea, low or high blood pressure

Neurological symptoms

Major symptoms: myoclonus, tremors, chills, rigidity, hyperreflexia

Minor symptoms: impaired co-ordination, mydriasis, akathisia

2. These symptoms must not correspond to a psychiatric disorder, or its aggravation, that occurred before the patient took the serotonergic agent.

3. Infectious, metabolic, endocrine or toxic causes must be excluded.

4. A neuroleptic treatment must not have been introduced, nor its dose increased, before the symptoms appeared.

*Adapted from Radomski et al[9]

Box 2: Major differential diagnoses[2,3]

Malignant neuroleptic syndrome
Infectious causes
Herpetic encephalopathy
Heat stroke
Myocardial necrosis
Delirium tremens
Intoxication by adrenergic or anticholinergic agents

Table 2: Most frequent distinctions between serotonin syndrome and neuroleptic malignant syndrome[2,3,8–10,17–20]

Characteristic	Serotonin syndrome	NMS
Onset	Sudden, within 24 h following introduction of a serotonergic agent	Slower, within 7 d following introduction of a neuroleptic agent
Symptoms	Agitation, diarrhea	Dysphagia, hypersalivation, incontinence
Signs	Dilated pupils, myoclonus, hyperreflexia	Hyperthermia (> 38ºC), akinesia, extrapyramidal "lead pipe" rigidity, rhabdomyolysis
Mortality	23 deaths reported until 1999*	15%–20%

Note: NMS = neuroleptic malignant syndrome.
*No percentage is reported in the literature, because there are too few cases.

Comment

The diagnosis of serotonin syndrome was straightforward in these 2 patients who presented with the classic triad of mental, neurological and autonomic signs and symptoms. This is one of the first instances in which 2 cases of serotonin syndrome are reported based on the revised Radomski criteria. This classification aids diagnosis by allowing for a quick evaluation of the seriousness of the situation. Discontinuation of causal agents and treatment of symptoms is effective. This syndrome must be prevented by educating patients to avoid self-medication, by limiting drug combinations and by improving compliance with "drug holidays."

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West Nile virus

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ß See related articles pages 1399, 1427 and 1455

Background: Since its arrival in North America in 1999, West Nile virus (WNV) has spread rapidly across the United States and into Canada. First detected in birds and mosquitoes in Ontario in 2001,[1] by the end of 2002 viral activity had been documented in Nova Scotia, Quebec, Ontario, Manitoba and Saskatchewan.[2] In the same year, cases of human infection were reported in Ontario and Quebec.[2]

WNV is a member of the Flaviviridae family, which includes the viruses responsible for Japanese encephalitis, dengue, St. Louis encephalitis and yellow fever. WNV infects over 150 species of birds as well as mammals such as squirrels, dogs, wolves, horses and mountain goats.[3] The Corvidae family of birds, which includes crows, blue and grey jays, ravens and magpies, are particularly susceptible to illness and death from WNV.[4] For this reason, sightings of dead crows have been used in Canada as a marker for WNV activity, and the testing of dead crows for WNV continues to be a fundamental part of an enhanced passive surveillance system.

Different types of mosquitoes are responsible for risk of disease in humans: "amplification" mosquitoes (e.g., *Culex pipiens* and *Culex restuans*), "bridging" species (e.g., *Coquillettidia perturbans*) and human biters (e.g., *Aedes vexans*). The first type feeds on birds and transmits the virus to other birds; this activity creates a large reservoir of WNV infection that starts to build in early spring. The second type of mosquito feeds on both birds and humans and is responsible for transmitting WVN to humans.[5] Twenty-eight public health units in Ontario conducted mosquito surveillance for the presence of WNV in 2002.[6] The most common species were *C. pipiens* and *C. restuans*, *A. vexans* and *C. perturbans*; however, field investigations found enough variation between adjacent health units to warrant local surveillance (Dr. Fiona Hunter, Brock University, St. Catharines, Ont.: personal communication, 2003). WNV-positive mosquitoes were identified in 19 Ontario health unit jurisdictions in 2002.[7]

Although mosquito transmission remains the most significant vehicle for human disease, WNV can also be spread through blood or organ donation,[8] pregnancy,[9] lactation,[10] needlestick injury and exposure to infected laboratory specimens.[11] In an update on WVN, the Canadian Blood Services stated that 2 cases of transmission are "almost certainly transfusion-related" and that another 2 are currently under investigation.[12]

WNV incubates for 3 to 14 days in humans; data from New York City indicate that only 20% of infected people have a febrile illness.[13] Clinical features range from fever accompanied by malaise, headache, myalgia, rash, lymphadenopathy, eye pain, anorexia and vomiting lasting for 3 to 6 days, to severe meningo-encephalitis. Severe muscle weakness and flaccid paralysis have been experienced by several patients admitted to hospital in the United States.[14] In addition, patients with neurological disease are experiencing long-term disability.[14] WNV should be considered in all patients with unexplained encephalitis and meningitis.[14]

Clinical management: Treatment of WNV illness remains supportive. For severe cases, intensive care and transfer to appropriate facilities is recommend-

Canapress

ed. West Nile encephalitis is typical of arboviral encephalitides, with a nonspecific prodrome leading to a deterioration in mental status, profound flaccid paralysis in some cases and coma in 15% of cases.[13,15]

Prevention and control: Prevention of WNV transmission to humans relies on the elimination of mosquito breeding sites and the use of personal protection. The experience in New York City, first with the eradication of malaria and then with the reduction of human WNV disease, demonstrates the role for habitat reduction through improved drainage and the necessity of municipal bylaws to prevent standing water.[16] These strategies require cooperation between public health, public works and conservation area officials and elected representatives.

Public education aimed at reducing the risk of mosquito bites has been conducted in Ontario, through the media, Internet, boards of education and pub-

Revised SARS case definition

The CDC surveillance case definition of severe acute respiratory syndrome (SARS) was revised Apr. 30 to include laboratory criteria for evidence of infection with the SARS-associated coronavirus (SARS-CoV). See *eCMAJ* SARS Web page for details (www.cmaj.ca/misc/sars.shtml).

lic health units. Reducing the number of breeding sites and using personal protection are key components of education campaigns. Recent surveys of residents in Ontario's Halton region, conducted June to October in 2001 and 2002, showed a significant increase in the proportion of residents who had taken measures to eliminate standing water on their property in 2002 compared with 2001 (63% v. 26%); however, less than 8% had consistently used an insect repellent containing DEET during outdoor activities (Rapid Risk Factor Surveillance System, Ontario: unpublished data, extracted Feb 2003).

Given the limitations of habitat reduction and public education to promote personal protection, control measures including the use of larvicides and adulticides to reduce mosquito populations have been used in the North American response to WNV. The key to any mosquito control program is good surveillance. Public health units in Ontario have relied on dead crow sightings, the testing of standing water for the presence of mosquito larvae and the trapping of adult mosquitoes for WNV testing to inform control efforts. Although evidence from randomized controlled trials is lacking, results from well-established mosquito control programs in Illinois and Louisiana have shown reductions in mosquito populations.[17,18]

Larvicides, often in granular, pellet or teabag formulations, are used in the spring and early summer to reduce the number of emerging mosquitoes. They are placed in catch basins and standing water sites that are close enough to human populations to pose a risk (see news article, page 1455[19]). (For larvicides approved for use in Canada, search the Pest Management Regulatory Agency's electronic database [www.eddenet.ca/b.asp; click on "ELSE label search" and enter "larvicide" in search box] or contact the agency by telephone [800 267-6315] or email [pmra_infoserv@hc-sc.gc.ca]). Each province regulates the sale, use, transportation, storage and disposal of federally regulated pesticides under its own provincial legislation. Two of the most common products used in North America as larvicides are biological agents (e.g., *Bacillus thuringiensis* var *israelensis* [commonly referred to as Bti] and *Bacillus sphaericus* [not yet available in Canada]) and growth regulators (e.g., methoprene).

Adulticides, used to kill adult mosquitoes and applied from ultra-low-volume equipment mounted on aircraft or trucks, are considered a final measure when other efforts have failed to reduce mosquito numbers, when human cases of mosquito-borne disease are increasing or when human health is at risk despite the use of larvicides and other environmental controls (Geoff Cutten, Insecticide National Steering Committee Team (INSECT) Subcommittee, Health Canada: personal communication, 2003). To date, most of the experience with WNV mosquito control has involved the use of resmethrin, a synthetic pyrethoid, and malathion, a rapidly degrading organophosphate.[20] Experience with malathion for medfly eradication in California has shown no human health effects.[21] However, malathion is highly toxic to insects, including bees, and to fish and aquatic invertebrates.[22]

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Nonnarcotic analgesic use and the risk of hypertension

Dedier J, Stampfer MJ, Hankinson SE, Willett WC, Speizer FE, Curhan GC. Nonnarcotic analgesic use and the risk of hypertension in US women. *Hypertension* 2002;40:604-8.

Background: ASA, acetaminophen and ibuprofen are the most commonly used medications among adults, according to a national survey of US households.[1] Short-term prospective studies suggest that NSAIDs can cause acute elevations of blood pressure,[2] and ASA and acetaminophen can influence prostaglandin homeostasis.[3] The Nova Scotia Heart Health study has shown that 21% of women aged 35–64 years have hypertension,[4] thus, even small elevations in blood pressure caused by nonnarcotic analgesic use could result in cardiovascular morbidity and mortality. To date, there has not been strong evidence of an association between nonnarcotic analgesic use and hypertension.[5,6]

Question: Is there an association between ASA, acetaminophen and other NSAID use and incident hypertension?

Design: Participants in the Nurses' Health Study[7] have completed a mailed questionnaire every 2 years, starting in 1976. The study by Dedier and colleagues is based on data collected between 1990 and 1998. In 1990, 85 625 women in the cohort returned the mailed questionnaire: 51 630 of them were included in the study, and the remaining women were excluded because of a reported history of hypertension (n = 27 344), chronic kidney failure (n = 10), failure to answer any of the questions on analgesic use (n = 336), no physical examination between 1988 and 1990 (n = 735) and no physical examination during the study period (n = 5570). The women were asked how many days on average each month they took any of ASA, acetaminophen or other NSAIDs. Dosage and prior duration of analgesic use were not ascertained. Body mass index (BMI), smoking status, age and physical activity were ascertained from the 1990 questionnaire and were updated with each subsequent biennial questionnaire. Alcohol and sodium intake were obtained from the 1990 questionnaire and again in 1994. Diabetes was diagnosed if it had been reported on any biennial questionnaire through 1990, and information on family history of hypertension was obtained from the 1992 questionnaire. Incident hypertension was determined based on answers in biennial questionnaires as to whether a physician had made a new diagnosis of hypertension in the preceding 2 years.

Incident rates were computed by dividing the number of new cases of hypertension by the number of person-years in that analgesic use category. Odds ratios were used as the measure of association. Multivariate pooled logistic regression allowed control for confounding factors, including concurrent use of other analgesic types. Subjects were censored after being diagnosed with hypertension or at the time of death.

Results: The median age of the cohort was 55 (interquartile range 49–61) years. The women who used ASA, acetaminophen or other NSAIDs at any frequency had a higher age-adjusted risk of hypertension than nonusers. The sizes of the odds ratios were similar across analgesic types by frequency of use. The relative risk of incident hypertension increased for all 3 categories of analgesic with increasing frequency of use, although it appeared to plateau over 14 days/month. This association remained after adjusting for age and after multivariate adjustment for age, BMI, sodium and alcohol intake, physical activity, family history of hypertension, diabetes and smoking status.

Commentary: This large prospective cohort study identified an association between the frequency of use of nonnarcotic analgesics and incident hypertension. The individuals studied were female nurses from the 11 most populous US states. The information on analgesic use was obtained from questionnaires. The definition of incident hypertension had previously been demonstrated to be highly correlated with the documented diagnosis of hypertension in the medical record.

There are limitations to this study. The Nurses' Health Study cohort is predominantly derived from the middle socioeconomic class and white. Of the women who answered the 1990 questionnaire, 32% reported having hypertension (and were excluded from the analysis) and a further 20% acquired hypertension during the subsequent 8 years. This combined rate is much higher than the 21% among women aged 35–64 years in the Nova Scotia Health Heart study.[4] It is not known when the hypertension was first noted. Comparisons were only carried out for each type of analgesic, and not with a group of nonusers of any drug. Doses and duration of analgesic use before 1990 and after 1992 are not reported.

Practice implications: This study does suggest that the risk of hypertension is increased by nonnarcotic analgesic use, but there still remain a number of questions concerning dose and duration of use and whether the use of analgesics is a surrogate marker for the conditions for which they were used. Some conditions that could be associated with hypertension could include premenstrual syndrome, headache, primary or secondary prevention of vascular disease, or arthritis.

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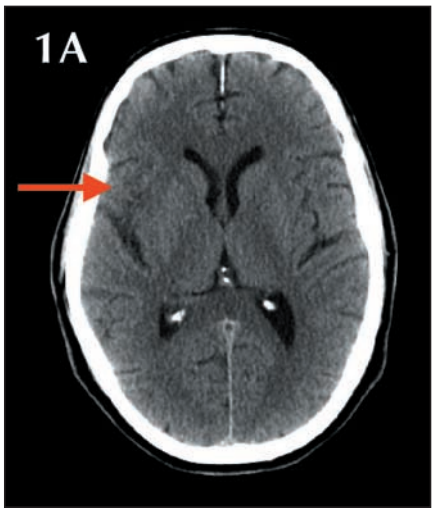
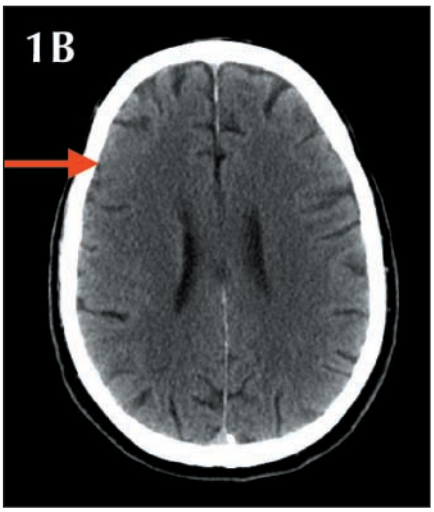
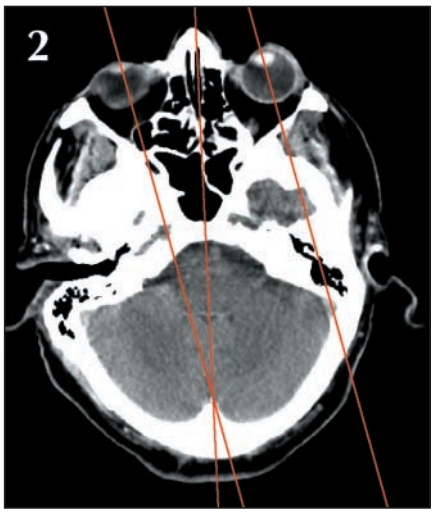
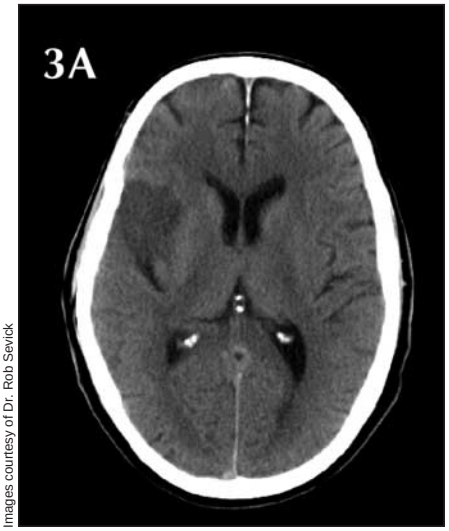
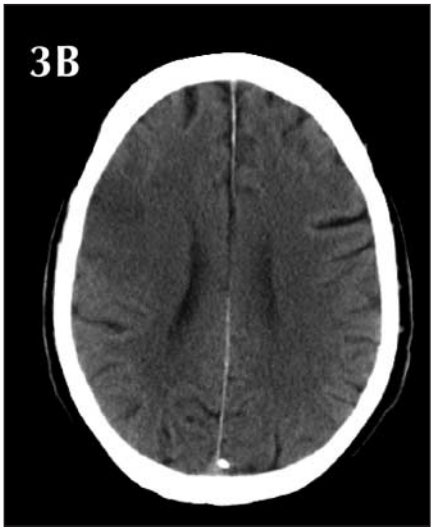
The eyes have it: conjugate eye deviation on CT scan aids in early detection of ischemic stroke











Images courtesy of Dr. Rob Sevick

A 65-year-old right-handed man, who had moved to Canada from Pakistan a year earlier, presented to the emergency department with a 75-minute history of "speech problems." The exact nature of his presenting complaint was difficult to assess because of a language barrier and the absence of a fluent translator. The man had a history of hypertension treated with atenolol and amplodipine and was taking ASA for a previous transient ischemic attack that had caused left-sided numbness.

Clinically he was noted to have a mild expressive dysphasia and slurred speech, which suggested a left cortical stroke. No conjugate eye deviation was observed. The remainder of his examination was unremarkable except for hypertension (191/85 mm Hg). The patient was rated as mildly affected on the National Institutes of Health Stroke Scale in the language category (NIHSS score of 1).[1] A non-contrast CT scan of his head performed 3 hours after symptom onset was described initially as showing no acute ischemic tissue (Figs. 1A and 1B; arrows demonstrate early ischemic changes that were appreciated later: loss of differentiation between grey and white matter and mildly effaced sulci in the right cortex and hypodensity of the right insula). The blood work and electrocardiogram yielded unremarkable findings.

The patient was treated conservatively and admitted for further tests and observation. By the next morning he clearly had sensory and visual neglect for the left side of his body, a left facial droop and dysarthria (NIHSS score of 4). Again, no eye deviation was detected on clinical examination. On review of the initial CT scan, however, conjugate eye deviation to the right was noted, and the ischemic changes were then appreciated (Fig. 2). A CT scan performed 20 hours after symptom onset confirmed a right frontal infarct in the right middle cerebral artery territory (Figs. 3A and 3B). Subsequent CT angiography revealed complete occlusion of the right common carotid artery with reconstitution in the petrous segment of the right internal carotid artery. The patient responded to rehabilitation therapy and was discharged home with minimal deficits.

Conjugate eye deviation, a sustained shift in horizontal gaze toward the af-

fected hemisphere, is a well-recognized finding in acute stroke. Several supranuclear lesions, such as in the cortical frontal eye fields or in the brainstem paramedian pontine reticular formation, can cause conjugate eye deviation.[2]

On CT scans, conjugate eye deviation or a lone abducting eye has been shown to reliably point toward the affected hemisphere in acute ischemic stroke.[3] Eye deviation observed on CT scans appears to be more common than is apparent on clinical examination. This is probably because most patients close their eyes during CT scanning, which removes fixation. Recognizing our patient's eye deviation might have allowed earlier recognition of his subtle right hemispheric ischemic changes (Fig. 1B).

When eye deviation is observed that does not agree with clinical information, the patient and CT scan should be examined carefully. In some cases eye deviation may be away from the side of the brain lesion and toward the symptomatic body side, such as in thalamic infarction and non-stroke diagnoses (e.g., seizure).

Most stroke patients have readily identifiable and localized symptoms and clinical signs, but when there is limited history or findings on physical examination, as in our case, the detection of eye deviation on a CT scan can help to identify the affected hemisphere.

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Concerns over lindane treatment for scabies and lice

Reason for posting: Scabies and lice infestations are common afflictions often remedied with topical therapies such as lindane,[1,2] a drug prescribed more than a million times last year in the United States.[3] However, lindane has several serious neurotoxic effects, ranging from dizziness, headaches and paresthesia, to seizures and even death.[4] The US Food and Drug Administration recently advised that these effects are more common in young children, elderly people and people weighing less than 50 kg and has recommended that the drug be used only as a second-line agent.[4]

The conditions: Scabies is caused by the mite *Sarcoptes scabiei*. The mites die if away from a human host for more than 72 hours.[5] Impregnated females (about 0.3 mm long) are transferred directly through close contact with people, bedding or clothing. They lay their eggs as they burrow under the skin, and after 3–4 days the larvae hatch and migrate to the skin surface, creating new burrows, where they mature into reproducing adults. Infestations often involve as few as 5–10 adult mites.[5] Elderly and immunocompromised hosts are at risk for a severe "crusted" form of scabies.[1,5] Initial infestations may be relatively asymptomatic for the first 4–6 weeks. In subsequent infestations, an intense, generalized, often nocturnal itch can develop within days. Pruritic lesions erupt along mite burrows in the finger webs, penis, breasts, and folds of the wrists, elbows and knees.[1,5] Secondary bacterial infections can occur, as can a papular rash on the buttocks, scapula and abdomen. Scabies is diagnosed clinically, aided by skin scrapings showing mites, ova or feces.[5] Treatment of asymptomatic close contacts is advisable to avoid reinfestation.

Head lice infestation (pediculosis capitis) is caused by *Pediculus humanus capitis*.[2,6] These lice live close to the scalp for easy access to blood and warmth and will die without a human host within 1–2 days. Adult lice are transferred through close human contact or through contact with hats and other headgear, pillow cases and clothing. Daily, female lice lay up to 6 yellow-white, 1-mm long

oval eggs, or nits.[6,7] Nits are cemented to the base of the hair shaft, typically within 6.5 mm of the scalp.[6] After a week, a pinhead-sized nymph hatches and, within a week, matures into an adult the size of a sesame seed.[7] Most infestations are asymptomatic, but local reactions to the louse saliva can cause a tickly or itchy scalp sensation. Secondary bacterial infections can occur. Close contacts should be checked and treated if infested.[8]

For scabies and head lice infestations, contaminated clothing and toys need to be laundered in hot water, or isolated in a plastic bag for 2 weeks or more.[2] Pets do not carry scabies mites or human lice.

The drugs: Lindane (gamma benzene hexachloride), a lipophilic insecticide, has been used since the 1950s.[4] Although most serious neurotoxic effects result from misuse of the product, one-fifth occur in patients using the drug appropriately.[4] At particular risk are elderly people, young children and people weighing less than 50 kg,[4] possibly because of increased systemic absorption and neurologic susceptibilities. Lindane is contraindicated in people with seizure disorders[4] and should be used cautiously in those at risk of seizures (e.g., people taking HIV treatments, antipsychotics, bupropion, systemic steroids, quinolone antibiotics or antimalarial drugs, and people with head injuries or intracranial lesions, eating disorders, or benzodiazepine or ethanol abuse).[4] Toxic effects can be minimized by applying small amounts of the drug for shorter than normal periods, by avoiding open sores, the eyes and the mouth, and by not repeating treatment or by maximizing the time between treatments.[9,10] Lindane is absorbed more rapidly into warm, wet or oily skin, or skin that is covered with occlusive diapers, shower caps or tight clothes.[10] Pregnant women should preferentially use alternative treatments (see below) but may use lindane cautiously if other therapies have failed or are inappropriate.[11] Breast-feeding women should pump and discard milk for at least 24 hours after using lindane.[9]

Several scabicides and pediculocides are commonly prescribed in Canada (Table 1). Local resistance, particularly of lice, to agents such as synthetic pyrethroids and permethrin may result in treatment failures.[12] DDT, malathion, carbamate agents and oral ivermectin are not available in Canada. Combining a topical treatment with an oral antibiotic (e.g., trimethoprim–sulfamethoxazole) may increase the success of head lice treatment.[13]

An alternative scabies treatment for pregnant or lactating women and children less than 2 months old is precipitated sulfur 6% in petrolatum.[14]

"Wet combing" — a nontoxic (but less efficacious) alternative to pediculocides — involves coating the scalp liberally with conditioner and removing lice and nits with a fine-tooth comb every few days.[6] There are limited efficacy data for the topical acetomicellar complex of acetic acid, citronella oil and camphor (SH-206)[8] or for formic acid preparations,[14] topical vinegar and mineral oil mixtures, or several herbal products.[14] A note of caution, however: "pound for pound" some "natural" therapies such as tea-tree oil may be more toxic to mammals than chemical treatments.[15]

What to do: Patients susceptible to scabies and head lice infestations include children and elderly people,[5,6] homeless people[16] and people in institutions,[1] and they may be the most vulnerable to the adverse effects of agents such as lindane.[4] Alternative agents may be preferable for first-line treatment in these and other cases. In the United States, patient exposure is being minimized by strict warnings on lindane product labels and limits on lindane package sizes.[4] It is unknown yet whether Canada will follow this lead.

Table 1: Prescription pediculocides and scabicides

Pediculocides*

1% permethrin (Kwellada-P Creme, Nix Dermal Creme)
Synthetic pyrethroid;† good ovicidal activity;‡ use with caution in children < 2 yr

Pyrethrin and piperonyl butoxide (R&C Shampoo)
Chrysanthemum extract;† poor ovicidal activity;‡ not restricted in children < 2 yr

Lindane shampoo (Hexit, PMS-Lindane)
Poor ovicidal activity;‡ contraindicated in neonates and people with seizure disorders; use with caution in pregnant and lactating women, children and elderly people

Scabicides*

5% permethrin (Kwellada-P Lotion, Nix Dermal Creme)
(See comments for 1% permethrin)

Lindane lotion
(See comments for lindane shampoo)

*Itch can occur after treatment and last weeks; it does not indicate treatment failure.
‡Retreatment is sometimes needed 7–10 days later; for lindane, optimal timing is unknown.
†Avoid in people allergic to chrysanthemums, pyrethrins or ragweed.

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The Left Atrium

A citizen's place is in the struggle

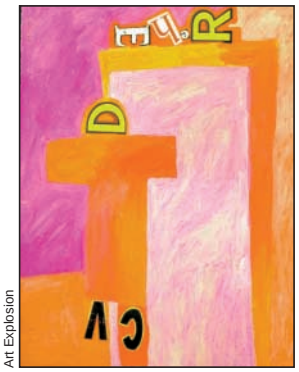
AIDS and the policy struggle in the United States
Patricia D. Siplon
Washington: Georgetown University Press; 2002
176 pp US$39.95 (cloth) ISBN 0-87840-377-9
US$21.95 (paper) ISBN 0-87840-378-7

Understanding how policy is made in a democratic society is undeniably germane to working in contemporary politics and medicine. In this book, Patricia Siplon presents an engaging account of the development of AIDS policy in the United States over the past two decades.

Policy-making is typically depicted as a relatively sterile process in which experts gather to identify and evaluate alternative solutions to a problem, and then select the alternative with the greatest benefits and least costs. Developing and implementing policies regarding AIDS, however, has never been so straightforward, and has at every stage been a struggle, as the title of this book suggests. This is partly because AIDS has disproportionately affected members of socially and politically marginalized communities, from the AIDS 4-H Club identified in 1983 by the US Centers for Disease Control as being at increased risk (homosexual men, heroin injectors, Haitians and hemophiliacs) to people of low socioeconomic status in sub-Saharan Africa today. These people have literally had to fight to get their issues on local and national political agendas, and then to advocate for their desired policies and outcomes.

Even beyond those infected with HIV and those directly affected by AIDS, people feel passionately about AIDS policy, whether while pushing for abstinence-only education for adolescents or while advocating for access to antiretroviral medications for people in the United States and abroad. AIDS brings up fundamental and value-laden issues: Is health care a right, or a commodity? How do we allocate resources in health care? Are people responsible (financially and morally) for the health outcomes of high-risk behaviours? How do we distribute burdens and benefits in society? When should the government intervene in or regulate the market? Who gets to make decisions? Answers to these questions set a precedent for other health and social policy issues.

In tackling this vast area, Siplon works methodically by chapter through several controversial policy areas: medical treatment, blood policy, HIV prevention, the Ryan White Comprehensive AIDS Resource Emergency (CARE) Act, and American foreign policy regarding AIDS in developing countries. Each chapter reads much like a magazine article that you would be delighted to find and would want to photocopy and share with friends and colleagues; Siplon draws on diverse sources and crafts a coherent story from disparate activities and developments throughout the United States and the world.



Art Explosion

Although Siplon focuses specifically on AIDS, she also illustrates ways in which the processes and outcomes of these struggles have altered the social and political fabric of the United States. Particularly noteworthy are the struggles for access to antiretroviral therapies such as AZT and to prophylactic medications such as pentamidine, and for compensation for people with hemophilia who were infected through contaminated blood products. In these cases, AIDS patients used self-empowerment — defined as "the idea that people can and should take on action roles for themselves, rather than allowing other people to act on their behalf or make decisions for them" — to organize politically and accomplish goals, even against the resistance of established institutions and individuals in government, the pharmaceutical industry and the medical community. The results of these actions have been an arguably unprecedented level of citizen involvement in both health policy-making and in medical treatment.

It is never easy to write about a contemporary political and social issue without the luxury of perspective that time affords. Nonetheless, Siplon demonstrates remarkable insight in finding and weaving together key perspectives and issues, including those of activists, which are traditionally ignored or understated.

I would recommend *AIDS and the Policy Struggle in the United States* to anyone interested in understanding how thousands of people's actions have had and impact on our understanding of AIDS and the development of AIDS policy, or in learning who the key players in health policy-making in the United States are. We can learn from the successes and failures of AIDS policy development, where the stakes are as high as lives and quality of life, and apply these lessons to current struggles surrounding AIDS and to other social and political issues.

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Faces and numbers

Condoms, fish & circus tricks: AIDS in Africa
A documentary film by Brenda and Robert Rooney
Rooney Productions, Lac-des-Loups, Que.; 2001.
VHS 53 min. $75 (institutions); $25 (individuals)
Available from info@rooneyproductions.com

Amidst the media flurry around SARS, it is easy to lose perspective. Though thousands are infected (and this number will certainly rise before it falls) the fatality rate of the disease remains at less than 10%. It is too early to tell how far the disease will spread, and how great the burden will be. The same is not true of another epidemic that defines the times: HIV/AIDS. Its toll is clear, it is high, and it is rising.

Numbers can numb our understanding: 30 million with HIV in sub-Saharan Africa; 3 million new infections there in 2002; 2.4 million deaths; 39% HIV prevalence in Botswana; 32% in Zimbabwe; 10 years until a vaccine. Zero cures.

Rooney Productions

It is nearly impossible to put this distant reality into a daily context unless you work in it. Visiting an AIDS village in Cambodia, home to a traditional healer famed for the success of his herbal HIV remedy, I was told that each of the 200 villagers had HIV (at least for now). Only as I walked through a village full of temporarily healthy young men and women and their lively children, did I understand the desperation that the people who have devoted their life to this immense problem must feel.

It seems a bold task to take this subject on, to try to get a hint of the reason behind the devastating expansion of HIV/AIDS. However, this is what two Quebec filmmakers, Brenda and Robert Rooney, set out to do with their documentary *Condoms, Fish & Circus Tricks*. Filmed in Malawi, South Africa and Zambia, their one-hour film attempts to do what statistics cannot: to put a face on AIDS in Africa.

The film opens on a busy market full of smiling people, some talking on cell phones, others laughing. One might imagine a similar scene in any country in the world; aside from the number of black faces, it could be Kensington Market in Toronto. The narrator soon intervenes with the sobering difference: "1 in 4 of these people has HIV."

The viewer is then introduced to the touchstones of the picture, the purveyors of the circus tricks of the title: a group of young South Africans, survivors of violence, trained by Cirque de Soleil as performers in the African Dream Circus. Throughout the film, the Rooneys return to this lively group of young men and women, showing footage of them performing their circus tricks, and asking them questions about what it means to be a young African in the time of AIDS.

The African Dream Circus is not the focus of this ambitious documentary, however. The Rooneys travel through villages and cities, talking with AIDS victims, interviewing authorities who are trying to thwart the spread of HIV, and taking footage of groaning hospitals and of villages filled with orphans.

Through these loosely tied images and vignettes, the Rooneys attempt to provide the viewer with a glimpse of both the magnitude of the problem and its complex etiology. The African Dream Circus performers hint at the distrust they have of a system that might offer testing, but no treatment. Why would they want to know if nothing can be done? The female director of an AIDS training program points to power dynamics between men and women that have accelerated the heterosexual transmission rate and threatened an African family structure that depends largely on the mother's healthy presence. But one of the most telling segments takes place in a rural fishing village, where we are introduced to Loveness Nkolola, a young African woman with a shy, broad smile. In a timid voice, she tells her story.

Narrator: Is this a good life?
Loveness: Yes, it is a good life.
Narrator: You were married here?
Loveness: Yes.
Narrator: How did you meet your husband?
Loveness: I came to buy fish.

But her husband is now dead. As a young, attractive woman, she was able to remarry. Her new husband says he is not worried about HIV. As the Rooneys move from the village, we witness the arrival of a large group of traders, men and women. We are asked to wonder how many infections will be traded with this commercial transaction in fish. By the time this film was finished, Loveness was dead.

Though the themes of this film are often difficult to sort out, the focus on the African Dream Circus and the many interviews with AIDS training program directors highlight what the Rooneys believe to be the solution to the crisis: education. Sexual education to prevent the spread of the disease, and basic education to strengthen the ability of young women to determine their destiny. We witness the street performance of two young men demonstrating how to use a condom to an even mix of amused, interested and offended faces. Gradually, young people in Africa are starting to talk about sex, and it is hoped that for growing numbers of young men and women, the message will reach them before the virus.

Several criticisms might be made of the cinematic merit of this documentary.

The viewer is asked to contend with a loosely connected series of narratives and is not always given much help in placing them into the larger context of this great puzzle. One gets the impression that the theses of the documentary were not clear to the filmmakers until the editing stage, and the lack of focus on such a complex topic leaves one with pieces too large to negotiate. Further, the political climate in South Africa, dominated by President Thabo Mbeki's reluctance to acknowledge several factors that contributed to the spread of HIV, is not touched on. Although we are shown the stark contrast of AIDS victims shivering for lack of antipyretics against the sterile world of a pharmaceutical trade show, a deeper discussion of access to essential drugs is omitted. Further, the cinematography is only of average quality and adds little to the gravity of the film, most of which is carried with the conversations contained in it. However, to focus on the shortcomings of this effort would be a disservice. The biggest drawback to this film is also the most important reason why it should be essential viewing for Canadians: the problem of HIV/AIDS in Africa is too large to be contained on screen, or in 53 minutes.

Though this reviewer is unfamiliar with the breadth and depth of similar documentaries, and cannot judge the merits of this one using comparisons, the subject alone warrants the inclusion of this film in Canadian libraries and perhaps on Canadian television. (It was aired in Canada on Vision TV in December 2002.) As the cases of SARS dwindle, their stories will fall from the front page, to the second, to the last, then out of the daily lives of Canadians. Just like HIV/AIDS has. For millions, though, HIV will be with them for the rest of their days. For them, the more documentaries like the overambitious *Condoms*, *Fish & Circus Tricks*, the more we will be reminded of the immensity of the problem and perhaps will be inspired to play a part greater than occasional witness.

During the making of the documentary, 10 million people were infected with HIV in sub-Saharan Africa. Midway through the film, a man with AIDS is interviewed, and asked what he might say to God about HIV if given the opportunity:

> I would [say] … please … this is a deadly disease … most of your people are suffering.

James Maskalyk
Editorial Fellow
CMAJ

Lifeworks

An inside view

Peter Lojewski has worked for almost 30 years as an emergency-room orderly. He had often thought of studying drawing or painting, but shift work made attending classes difficult. In 1989, Lojewski spent his summer vacation in the northernmost part of British Columbia at the Atlin Art Centre, a school that meshes art with adventure and stresses working from one's own experience. He filled a large sketchbook with drawings, including some done from memory of his work in the Royal Columbian Hospital in New Westminster, BC. Three weeks of intense creative work allowed him to begin the process of expressing his ideas and observations.

A selection of Lojewski's paintings and a mixed-media construction were exhibited last fall in the group show, *Satan, oscillate my metallic sonatas*, held at the Contemporary Art Gallery in Vancouver Nov. 14, 2002, to Jan 5, 2003. An inordinately shy and gentle man, Lojewski portrays the hospital as a complex and often frightening world. He says it is not his intention to alarm people, but to present hidden aspects of the hospital. Procedures, equipment, the relentless pressure to deal with a constant stream of people, tragedy and even hilarity all find their way into his visual world.

In 1995 Lojewski began to create acrylic paintings from his sketches. In *Code Blue*, a doctor, a resident and several nurses stand around the bed of an older man. His belly is distended and his chest is sunken. Lojewski paints himself into the centre of the image, performing cardiopulmonary resuscita-

Courtesy of the artist

Peter Lojewski, 1996. *Modern Hospital* (detail). Styrofoam, aluminum, various materials, found objects. Acrylic 20″ × 33″ × 18″.

tion. All the figures are separate from one another, except that Lojewski's hands bear down on the man's chest. Two nurses seem removed from the event, walking through or out of the image. The scene is one of alienation, pathos and perhaps even futility. There is also a sense of the workaday world in which people follow usual procedures despite the urgency of the scene.

In a larger painting entitled *Modern Medicine* (1996), *Code Blue* has been adapted and incorporated into the upper half along with an intensive care unit and a diagnostic facility. The bottom half features a morgue. Lojewski aims for a high level of accuracy. Sometimes he takes photographs or makes careful sketches to record details of medical equipment. The crypts in the morgue are marked with tags — green for empty, red for full; one space ominously gapes open. Lojewski also adds fictitious elements: a chute descends into the morgue, and a door at the back opens to a blue sky with friendly clouds. Poised to exit, figures shrouded in white lie on stretchers by the door. In the morgue, a naked figure awaits an autopsy while someone in medical garb approaches with an electric circular saw. This is a modern vision of the underworld.

In his understated way, Lojewski says that some days at the hospital bring "everything at once." Packed into a small canvas, *Emergency Room* (1996) explodes with lurid colour and frenetic activity. Figures sprout tubes, vomit, knock over lab carts. The breakneck pace extends beyond the room: through a window the viewer sees an ambulance unloading still more patients. Amidst all this activity Lojewski still captures the vulnerability of the naked figure.

A calmer but still pointed commentary, the construction *Modern Hospital* (1996) is made from salvaged materials. Styrofoam walls open to reveal a variety of silver foil-lined wards. A janitor's torso emerges from the floor. (Lojewski remarks that this hospital has spent all its budget on technology and is left with half a janitor.) Hospital beds have buttons for wheels, and the helicopter on the roof is fashioned from a battered pop can, its rotors comically (or ironically) cut from tattered aluminum. Outside, the back end of a toy horse protrudes from a wall, and withered miniature shrubs announce the entrance. Fellow workers brought Lojewski things he might use for his project, including a plastic dinosaur and some action figures. Great muscle-bound hemen recline on beds while their beefy friends visit. There is a sense of camaraderie despite the evidence of what chronic underfunding has done to the medical system.

If a doctor practises without proper training, he or she is a hazard. Yet in art, all the training, perspective drawing and art theory in the world will not amount to much without the artist's willingness to offer an intimate and honest expression. Although Lojewski's art might be dismissed by some critics as "primitive" or "naive," he is not ashamed to bear these labels. By bringing an unpretentious and unflinching gaze to his artmaking, Lojewski allows us a glimpse into the turmoil of his working life.

Courtesy of the artist

Peter Lojewski, 1996. *Emergency Room.* Acrylic, 16″ × 20″.

Courtesy of the artist

Peter Lojewski, 1996. *Modern Medicine.* Mixed media on canvas, 40″ × 30″.

Bettina Matzkuhn

Ms. Matzkuhn is a fibre artist and craftsperson based in New Westminster, BC. She is currently an MA student in Liberal Studies at Simon Fraser University, Vancouver, BC.

Larvicide debate marks start of another West Nile virus summer

Published at www.cmaj.ca on May 6, 2003

As Canada prepares for what is becoming an annual battle against the West Nile virus (WNV, see page 1427), another battle is developing over the best way to respond to the emerging threat.

For instance, Toronto and other Ontario municipalities plan to employ a larvicide — methoprene — that New York City (NYC) is wary of using. The New York Environmental Protection Agency is limiting use of the synthetic growth hormone, which prevents mosquitoes from becoming adults, because of concerns it may affect other species. The agency allows its use only in water that eventually flows into purification plants; Ontario permits its use in storm sewers, many of which flow into natural waterways without the water being treated.

New York's concerns are shared by some Toronto politicians. Michael D'Andrea, Toronto's manager of infrastructure asset management, told city council that when it rains, water from storm sewers and catch basins is flushed directly into streams and creeks, where methoprene "may have adverse impacts on other insects and aquatic organisms."

However, the US Environmental Protection Agency reports that methoprene "does not pose unreasonable risks" to human health and that it presents "minimal acute and chronic risk" to freshwater fish and invertebrates."

In Canada, the Pest Management Regulatory Agency (PMRA) says methoprene is "practically nontoxic to mallard ducks and only slightly toxic to fish." Although it is "very highly toxic to freshwater invertebrates," it has no lasting adverse effects when used properly.

Councillor Joe Mihevc, chair of Toronto's Public Health Committee, says the city is concerned about the larvicide's spread to urban wetlands. That's one reason why New York City, which has coped with WNV since 1999, uses bacterial larvicides that target only mosquitoes. (The bacteria secrete an enzyme that kills the insect.) But not all bacterial larvicides are available here. The PMRA says no one has applied to license *Bacillus sphaericus*, the larvicide NYC is using.

In April, Quebec used another bacterial larvicide that has been approved for use, *Bacillus thuringiensis* var *israelensis* (Bti). "We are trying to contain the outbreak without harming the environment," says government spokesperson Collette Gaulin. Methoprene will be used "if absolutely necessary." Bti is effective only in water that contains organic materials, such as plants. *Bacillus sphaericus* can be used in any water.

Ontario has accounted for 17 of 18 of Canada's WNV-related deaths and 307 of its 325 confirmed cases. There have been 16 cases in Quebec and 2 travel-related cases in Alberta.

Ontario has asked every municipality to consider using a larvicide, says provincial spokesman Paul Kilbertus, but "we don't tell them when and where to do things."

In February, Toronto city council earmarked $688 000 for WNV control, including $360 000 for the methoprene pellets that will be used in 175 000 catch basins.

Health Canada expects WNV to reach British Columbia and the Yukon by the fall. "Educating the public on avoiding mosquito bites is the most important thing," says epidemiologist Peter Buck, and education accounted for a large part of the WNV strategy that Health Canada announced in April.

Prevention is the key

"Public education has been quite successful and will continue," says James Gibson, NYC's assistant commissioner for veterinarian and pest control services. "Prevention is the primary goal."

The US Centers for Disease Control and Prevention (CDC) says that less than half of Americans surveyed last year took any precautions against mosquito bites, and only about a third used a repellent containing N,N-diethyl-3-methylbenzamide (DEET), which is considered to offer the best protection.

Last year, more than 4000 Americans became ill because of WNV and 274 died. There were human cases in all but 11 states. WNV specialist Lyle Petersen of the CDC says tackling the virus is "unbelievably complex." The one certainty is that "where West Nile has been, it stays." — *Barbara Sibbald*, CMAJ

Ontario chooses FP as CMA's president-elect

Ontario physicians have chosen an FP from Brampton as their nominee for CMA president-elect in 2003/04 (see *CMAJ* 2003;168[9]:1170). If Dr. John Tracey's nomination is confirmed by General Council, he will assume the presidency in August 2004, when the CMA's annual meeting is hosted by the Ontario Medical Association (OMA).

Tracey, who graduated from the University of Dublin in 1971 and is a founding member of the Coalition of Family Physicians of Ontario, was the only 1 of 6 candidates for president-elect who had not served as president of the OMA. He acknowledged his outsider status in an address following the election, praising the OMA board for allowing members to vote "in an open and democratic fashion." Tracey defeated Drs. Elliot Halparin, Albert Schumacher, Kenneth Sky, Ronald Wexler and Michael Wyman. — *CMAJ*

BC begins its WNV countdown

The Rocky Mountains have provided some protection so far, but as summer approaches British Columbia is bracing for the arrival of West Nile virus (WNV).

Dr. Murray Fyfe, an epidemiologist with the BC Centre for Disease Control (BCCDC), says that mapping of the virus in North America indicates that mountain ranges offer some protection, but once that barrier is breached he expects the virus to spread unimpeded along Canada's West Coast. WNV was found in dead birds in neighbouring Washington State late last summer.

BC has already designated WNV infection a reportable disease, and a multiagency provincial plan emphasizes tailor-made responses for different regions. Sparsely populated areas may be employing only public education campaigns, says Fyfe, while mosquito-control measures, such as placing larvicide pellets in breeding locations or eliminating these sites, will be used in heavily populated areas when practical. Water in natural reservoirs such as lakes cannot be treated without provincial authorization. Spraying insecticides is considered a last resort, but the use of larvicides in pellet and other forms could begin this month. Public education to prevent mosquito bites and breeding in people's yards has already begun. "I'm hoping the integrated approach is the way to go," says Fyfe.

Dozens of mosquito traps were set up around the province in May, and the samples will be sorted by species and tested at the BCCDC.

Fyfe says it is impossible to predict WNV's impact. "They say this will take many months, if not years. We don't fully understand the ecology of the virus in North America, and it behaves differently in different places. We are going to do what we can this year, and based on what we find, we will revise our plan for the coming years."

He says WNV poses a difficult public health challenge. "On the one hand we don't want to minimize this, [but on the other hand] you want to put it into perspective so that people don't think they shouldn't go camping anymore because they may come across a mosquito. But that balance will be difficult to reach." — *Heather Kent*, Vancouver

As SARS toll climbed, so did economic cost to Toronto

No one yet knows Canada's final health toll from severe acute respiratory syndrome (SARS), but officials in Ontario already know the financial tab will be huge.

As soon as news broke about the first fatalities — a Chinese mother and son living in Scarborough — consumer traffic in the city's Asian communities dropped precipitously. Businesses in both of Toronto's downtown-area Chinatowns and in the Pacific Mall have reported traffic decreases of between 70% and 90% since the outbreak began in mid-March. In fact, things had become so unsettled by early April that Prime Minister Jean Chrétien and other politicians trekked to Chinatown in an attempt to prove it was safe.

Canapress

Business as usual? The prime minister visits Toronto's Chinatown

The same anxiety led to shortages of face masks and antibacterial soap at many drug stores and medical supply firms. The subsequent images of masked city workers, when combined with intense media coverage, led to a rash of conference cancellations. Hotels reported millions of dollars in cancelled reservations, including 1 major cancer care convention. By late April, Toronto was an international pariah, with countries around the world — and the World Health Organization — issuing travel advisories. Harvard University told its faculty members not to travel to Toronto, while Wal-Mart restricted travel to the city for its American executives.

Entrepreneurs were quick to cash in — SARS travel protection kits, which included masks, gloves, pocket-sized bottles of hand wash and herbal remedies to boost the immune system, were soon selling on the Internet for US$49. — *Brad Mackay*, Toronto

Police still investigating sniper attacks on MDs

James Kopp has been found guilty of murdering New York state obstetrician Dr. Barnett Slepian, but police are still trying to close other cases involving Canadian physicians who were shot.

Kopp remains a suspect in the nonfatal shootings of physicians who provided abortions in Winnipeg, Vancouver and Ancaster, Ont. He has been charged in the last case — Dr. Hugh Short was shot in the right arm as he sat in his home Nov. 10, 1995 (*CMAJ* 1998;159[9]:1153-5) — but there is insufficient evidence linking him to the Winnipeg or Vancouver cases.

"The important thing for us is to get closure for the victims here," says Winnipeg police Inspector Keith McCaskill, who serves on a national task force created to solve the crimes. McCaskill, who is working with state and federal prosecutors in the US, says Kopp probably won't be tried for his Canadian crimes because the murder in the US takes precedence.

Kopp, 48, is expected to be sentenced this month to life imprisonment with no parole eligibility for 25 years. That could change, because he also faced additional federal charges that may eliminate the possibility of parole.

Kopp admitted shooting Slepian in his suburban home near Buffalo on Oct. 23, 1998. Slepian, 52, was the last of 7 Americans killed in attacks on abortion clinics and abortion providers from 1993 to 1998. — *Barbara Sibbald*, CMAJ

SARS poses challenges for MDs treating pediatric patients

When health officials unveiled a case definition for severe acute respiratory syndrome (SARS) recently, it was supposed to help MDs decide if patients had a disease for which there was no test.

But the comprehensive list of symptoms, which include fever and a dry cough, posed a unique problem in Toronto's already stressed ERs. How could they diagnose SARS in pediatric patients who could not tell them about their symptoms?

"Ultimately, we're faced with gazillions of kids with runny noses, fevers and coughs from any of a variety of non-SARS sources," explained Dr. Bruce Minnes, associate clinical chief of emergency medicine at the Hospital for Sick Children. "So when should we have a higher suspicion?"

In the absence of a suitable test, said Minnes, doctors at Toronto's 15 emergency departments and 5 SARS assessment clinics started relying on a combination of symptoms and background information provided by a parent.

Information about travel to affected countries, or exposure to an affected community within Toronto, raised a red flag. "With any kid who has the usual mild respiratory symptoms or fever, contact screening is our tool for identifying someone who may be at risk."

When young patients show additional severe respiratory symptoms and higher fevers, doctors automatically began treating them as SARS patients. "We would err on the side of caution, because we obviously don't have a tool for making a positive diagnosis."

This means that children showing symptoms will be more likely to undergo mandatory 10-day isolation than adults, but Dr. Tim Rutledge defended such moves. "We want to be really careful," explained the medical director of emergency services at the North York General Hospital. "Specifically, with children and the frail elderly the presentation can be more subtle, and therefore we have to be even more hypervigilant."

Rutledge estimates that children have accounted for 20% of the suspected or probable SARS cases at his hospital. Global experience has shown that while these pediatric diagnoses are harder to make, most fatalities occur in older patients. Of Toronto's 23 SARS deaths up to May 1, none of the patients has been under 39, and most have been older than 70. "It definitely seems to be a less severe illness in children," Rutledge said.

Canapress

Children: Best to err on the side of caution

He said MDs should look for a combination of symptoms and test results before isolating a child; the most useful signal from the physical exam is a temperature above 38° C. Both doctors said the prospect of placing an infant or toddler in quarantine is stressful. "It's not a great position to be in," said Minnes. — *Brad Mackay*, Toronto

Alberta: growing, greying and facing rising health care costs

Alberta physicians topped the $1-billion mark in total fee-for-service billings in 2001/02, an increase of more than 10%. Annual payments averaged more than $208 000, an increase of nearly 6%.

Those numbers were among a flood of data released in the *2001/2002 Alberta Health Care Insurance Plan Statistical Supplement*. The annual report indicates that more people are using health services and more doctors are delivering them. As well, drug costs have nearly doubled in 4 years.

Alberta Health spokesperson David Dear said population growth and a growing number of doctors account for most of the increase in fee-for-service payments. Alberta Medical Association President Steve Chambers added that a recent 3-year deal that increased physicians' fees by nearly 22% also had an impact.

Chambers defended the raise, arguing that "it makes it more attractive for a physician to come here and stay here." He says that with only 20% of Alberta doctors accepting new patients and with the average age of doctors approaching 50, incentives are needed to avert a crisis.

The report also warns of potential problems regarding drugs costs. In 2001/02, Alberta paid nearly $350 million for prescription drugs, an 89% increase from 1997/1998, when drugs cost $185 million. Dear said drugs now cost the province $1 million per day, and that will grow by 17% to 20% in 2003.

Five years ago, Alberta struck a committee cochaired by a physician and a pharmacist to study cost containment. One of several measures to emerge is the "checkpoint program" for first-time prescriptions of 30 days or more duration. In an effort to reduce waste, the drug plan now approves only a 7- to 14-day trial first to ensure the drug works.

The province has also instituted an "academic detailing program" that allows physicians to get advice from designated pharmacists regarding the range of drugs available. It's supposed to stop MDs from relying on a single therapy when more efficient ones are available. One drug, omeprazole, accounted for 6% of government drug spending in 2001/02.

Modern medicine faces a quandary, Chambers said. Drug companies are marketing effective new products, but they are expensive and they also keep people alive longer. Seniors are healthier and more active than ever, and Chambers said the rising costs are a sign of this.

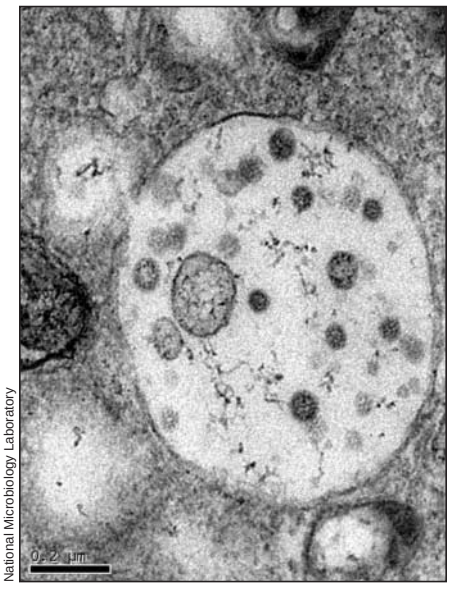
Dear said drug costs can't be viewed in isolation. "They bring enormous value to the system in the good they do for patients, and they represent a kind of savings to the system by keeping patients out of it." — *Lisa Gregoire*, Edmonton

SARS may have a silver lining, WHO says

Severe acute respiratory syndrome (SARS) is proving one of the most intriguing challenges facing scientists in the 21st century, the director general of the National Microbiological Laboratory in Winnipeg says.

Speaking at the first North American meeting on SARS, which ended in Toronto May 1, Dr. Frank Plummer said the coronavirus, which the World Health Organization (WHO) says causes SARS, is also being found in some people who are neither probable nor suspected SARS patients. Among those who fit into the probable category, the proportion of people who are testing positive for the virus has been declining, from 80% to 40%. However, the coronavirus is also being found in about 14% of people under investigation for SARS but who fail to meet the clinical definition of the disease.

Plummer is part of the 58-member Canadian team that published the 29 751-base genome sequence of the virus known as the Tor2 isolate, which is unlike any of the 3 previously known groups of coronaviruses (*Science* [online] May 1;10.1126/science.1085953). The genome sequence will aid in the diagnosis of SARS infection in humans and potential animal hosts, and it will speed the development of antiviral weapons and the identification of structural targets for vaccine development, the researchers report.



National Microbiology Laboratory

Cultured cell infected with coronavirus

Among the 20 probable and 40 suspected SARS cases reported so far in the US, 6 people have tested positive for coronavirus infection. Stephen Ostroff, deputy director at the US National Center for Infectious Diseases, says polymerase chain reaction diagnostic kits will be distributed throughout the US as part of the containment effort. Although WHO remains convinced that a coronavirus is the culprit behind SARS, the US Centers for Disease Control and Prevention suspects additional viruses and medical conditions are involved.

Fighting the new disease will be an ongoing challenge. Arlene King, Health Canada's director of immunization and respiratory infections, says the role of airborne transmission is still unclear, but stringent application of airborne, contact and droplet precautions appear to provide effective protection for caregivers.

Transmission may occur during the prodromal period, when only early symptoms such as malaise or myalgia are present, and it can also occur even 10 days after the serious symptoms, such as high fever, have resolved. Transmission from an asymptomatic patient is considered very unlikely.

King recommends a staged approach to SARS, along the lines of the pandemic influenza model. Following an initial alert for outbreak outside of Canada, the focus will be on information gathering and enhanced surveillance to detect community spread, even as cases involving travellers and their close contacts are addressed through isolation, quarantine and contact tracing.

In Canada, the SARS crisis has led to a drastic rethinking involving Canada's public health network. Gerald Dafoe, CEO of the Canadian Public Health Association, says Ottawa must start devoting 5% to 6% of its health budget to hiring more health care workers in order to improve the country's ability to respond to public health crises. Dr. Donald Low, chief of microbiology at Mount Sinai Hospital in Toronto, couldn't agree more. He says the recent crisis forced Toronto to draw call for help across the country to cope with the patient overload. Dafoe also says the Canada Health Act should be amended to make public health an essential service.

The problems that face Canada when a disease such as SARS begins it international sprint were put into perspective by Ronald St. John, director general of Health Canada's Centre for Emergency Preparedness and Response. He pointed out that Canada has 100 million land border crossings each year, and 40 000 people fly from Toronto daily. This means there is a danger that Canada will both import and export disease. He said new diseases will result in new public health interventions, ranging from health declarations and visual screening to medical interviews, temperature or thermal screening, and even drastic measures such as quarantine camps.

Despite all the bleak news that has emerged because of SARS, WHO's executive director of communicable disease programs managed to find a silver lining. Dr. David Heymann says the lessons learned and global public health intelligence network that has emerged because of SARS will make it easier to track the next infectious disease that emerges. — *Sridhar Nadamuni*, Toronto

Gender gap in life expectancy narrows to 5.2 years

The gap in life expectancy between men and women is closing, Statistics Canada says.

Data from 2000 indicate that life expectancy at birth — a fundamental indicator of population health status — increased slightly to new record highs for both sexes in 2000. A female born in 2000 can expect to live 82 years, up 0.3 years from 1999. The life expectancy of a male born in 2000 is 76.7 years, up 0.5 years in the same period. The gender gap has narrowed from 5.4 years in 1999 to 5.2 years in 2000.

Statistics Canada also reports that the number of deaths declined by 0.7% from 1999 to 2000, the first decrease since 1981. In 2000, 218 062 people died in Canada — 111 742 males (down 1.7% from the previous year) and 106 320 females (up 0.4%).

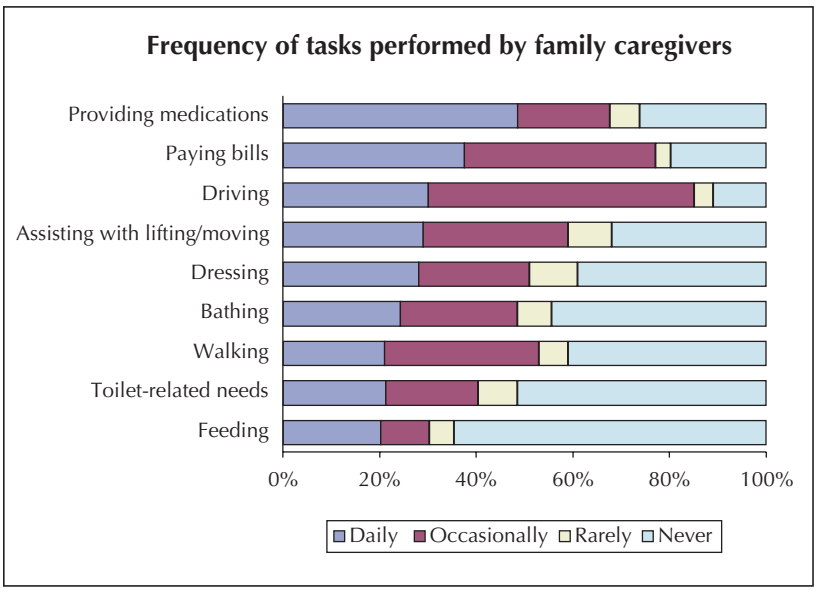
The 2 main causes of death were diseases of the circulatory system (nearly 35%) and cancer (29%). — *CMAJ*

PULSE

Burden of home care borne by women

A recent survey found that about 4% of adult Canadians currently care for a family member who is frail, chronically ill or has a physical or mental disability. More than three-quarters (77%) of these family caregivers are women, and 48% are aged 55 or more. Thirty-one percent of family caregivers are retired, and another 16% are full-time homemakers; 47% are employed or seeking work. One-fifth of caregivers have been providing care for 11 years or more, and an additional 17% have been doing it for 6 to 10 years.

Recipients of family care are most likely to be a spouse/partner (38%) or parent (33%) of the caregiver, while 17% are children of the caregiver. More than half (57%) of the recipients of care are 65 and older, while 9% are under 18. Forty-three percent of care recipients require assistance because of physical disability, 21% because of mental disability and 18% because of a combination of physical and mental disability (18% of respondents did not specify).



The large majority of caregivers (83%) say they have the necessary skills to handle their care-giving activities, although many say they could use help for a variety of activities, either to provide respite care (15%), bathing (10%), general in-home care (10%) and cleaning or housework (7%). While 43% of caregivers say they are coping very well with their responsibilities and another 49% say they are generally coping, more than two-thirds (70%) indicate that providing care has been difficult or stressful. Among those reporting stress, 77% say they have had problems with their own emotional health, 54% with personal finances and 50% with physical health.

The *National Profile of Family Caregivers in Canada — 2002: Final Report* is available at **www.hc-sc.gc.ca/english/care/nat_profile02/1.html**. — *Shelley Martin*, Senior Analyst, CMA Research, Policy and Planning Directorate

Number of countries with nationwide smoking restrictions growing

Norway has joined a growing list of countries by implementing national antismoking measures. In April, the Norwegian parliament voted to outlaw smoking in bars and restaurants beginning in spring 2004. In Canada, restrictions vary across the country because they are not a federal responsibility.

"We have 1 message: employees in restaurants and bars should have the same protection against passive smoking as other employees," says Ellen Juul Andersen of the Norwegian Medical Association. Andersen, vice-president of Tobacco-Free, helped lead the lobbying drive.

"We can see that it can be a little bit difficult for some bars to become smoke-free, but … there will be educational programs," Andersen told *CMAJ*.

Bans on smoking in public places have been — or will be — implemented in Ireland (January 2002), Zimbabwe (October 2002), Thailand and Pakistan (November 2002), Romania (December 2002), Iran (sometime in 2003), and Uganda and Sweden (2004).

Greece, where 45% of the adult population smokes, banned smoking in many public places last September. Fines were introduced in December for cafés, bars and restaurants in which owners failed to allocate at least half the space to nonsmokers.

In April, a Labour MP in the United Kingdom introduced a private member's bill to ban smoking in cafés and restaurants. It will receive second reading in July. And Bhutan, a country of 2.1 million people nestled between India and China, aims to become the first nation to ban tobacco use entirely. According Health Minister Sangay Ngedup, "The great saint who brought us Buddhism … said smoking was bad and no follower of Lord Buddha should smoke. He may have been referring to opium, but we feel very comfortable extending his concerns to tobacco." As of January, 18 of Bhutan's 20 districts had banned tobacco sales.

Japan implemented a smoking ban in sections of central Tokyo in November 2002, but it was a response to the number of people being burned on the crowded streets, not to concerns about second-hand smoke. — *Barbara Sibbald*, CMAJ

Deaths

Nécrologie

Notice — *CMAJ* welcomes obituaries submitted within 60 days of a death. These should be no longer than 200 words, and colourful writing is encouraged. Send to Patrick Sullivan, **patrick.sullivan@cma.ca**; fax 613 565-2382.

Archambault, Jean, Sainte-Adèle (Qué.); Université de Montréal, 1949; anesthésie; FRCPC; ancien membre du personnel de l'Hôpital Ste-Jeanne D'Arc. Décédé le 19 janvier 2003, à l'âge de 80 ans; laisse son épouse, Simone.

Brajac, Josip, Sarnia, Ont.; University of Zagreb (Yugoslavia), 1953; MCFP; former staff, St. Joseph's and Sarnia General hospitals. Died Jan. 26, 2003, aged 81; survived by 4 children.

Brown, Leigh B., Edmonton; University of Alberta, 1944; obstetrics/gynecology; FRCSC; former staff, University Hospital and Cross Cancer Institute; consultant, Royal Alexandra Hospital; director, gynecology, Cross Cancer Institute; clinical professor, University of Alberta. Died Dec. 27, 2002, aged 83.

Button, James R., Ridgetown, Ont.; University of Western Ontario, 1949; former staff, Public General and St. Joseph's hospitals. Died Jan. 23, 2003, aged 76.

Campbell, Ivor D., Victoria; University of Edinburgh (Scotland), 1950; FFARCS; former chief, anesthesia, Prince Edward Island and Charlottetown hospitals; staff, Queen Elizabeth Hospital Incorporation. Died Jan. 3, 2003, aged 77; survived by his wife, Hope, and 2 children.

Drever, George F., Edinburgh, Scotland; University of Edinburgh, 1966; former staff, Chilliwack General Hospital. Died Jan. 11, 2003, aged 61.

Isaac, Jacob E., Winnipeg; University of Manitoba, 1940; general surgery; FICS, FRCSC; former staff and chief of surgery, Misericordia and Concordia hospitals; 1 of 5 original members of Winnipeg Clinic and remained on staff for 54 years; senior member, CMA. Died of metastatic cancer Jan. 5, 2003, aged 88; survived by his wife, Agnes, and 2 daughters. Peter Harder commented: "He arrived from Russia as a child in 1924, and was blessed by having many of his dreams realized."

Kelly, Peter, York, Ont.; University of Sheffield (England), 1949; MRCS, LRCP, FRCP; pilot, RAF, WW II; former staff, Bellwood Health Services, Humber River Regional and Credit Valley hospitals. Died Jan. 15, 2003, aged 77; survived by his wife, Dorothy, 1 daughter and 1 stepdaughter. "When his office closed for the day he would go straight to the Maple Airport and head for the sky. Now, he has taken his last solo flight."

MacWatt, David J., St. Catharines, Ont.; University of Edinburgh (Scotland), 1943; anesthesia; CRCPC; FRCPC; RAF, WW II; former staff and chief, anesthesia, Lakeshore General, St. Catharines General and Hotel Dieu hospitals. Died Jan. 23, 2003, aged 88; survived by his wife, Freda, and 2 children.

Manning, R. Elizabeth, West Vancouver; University of Toronto, 1956; former assistant medical officer, Vancouver Health Unit. Died Jan. 21, 2003, aged 70; survived by her husband, Jack Edwards, and 3 children.

Mason, Robert J., Windsor, Ont.; University of Western Ontario, 1959; psychiatry; FRCPC; former staff and chief, psychiatry, Windsor Western Hospital Centre; lifetime member, OMA. Died Jan. 16, 2003, aged 75; survived by his wife, Joan, and 3 daughters. "He was an avid collector of model trains."

McIntosh, Alan D., Kelowna, BC; University of Toronto, 1953; MCFP; former staff, Kelowna General Hospital. Died Jan. 15, 2003, aged 80; survived by 5 children. "He practised in Kelowna for over 30 years and especially enjoyed his sunny afternoons at the Kelowna Golf and Country Club."

Merchant, Nigel, Halifax; Dalhousie University, 1975; ABEM; former staff, Queen Elizabeth II Health Sciences Centre–Victoria Site; emergency medicine staff, Victoria General Hospital; civilian physician, CFB Stadacona. Died Nov. 25, 2002, aged 58; survived by his wife, Joyce, and 3 children. "He loved to teach, especially in laboratory and prehospital medicine. He gave freely of his time and expertise to those who needed them."

Oszadszky, Sandor, Rossland, BC; Budapest University (Hungary), 1951; diagnostic radiology; FRCPC; former head, radiology, Trail Regional Hospital. Died Jan. 14, 2003, aged 76; survived by his wife, Maria, and 3 children. "He escaped from Hungary on foot and entered Canada as a refugee through Gander, Nfld. He started this new chapter by cleaning floors before repeating years of training. He was the sole radiologist in Rossland, Trail, Castlegar, Grand Forks and Creston until 1986. He practised until his retirement in 1993, having missed only 1 day of work."

Riedweg, Edward A., Edmonton; University of Alberta, 1965. Died Jan. 17, 2003, aged 61.

Rutherdale, John A., Burlington, Ont.; University of Toronto, 1950; internal medicine; FACP, FRCPC; former medical consultant, Toronto Rehabilitation Centre; medical director, Financial Life Assurance and American Life Insurance companies; clinical teacher, University of Toronto. Died Jan. 22, 2003, aged 76.

Stubbing, David G., Burlington, Ont.; University of London (England), 1970; respirology; MRCP, FRCPC; former director, respiratory rehabilitation, Hamilton Health Sciences Corporation–Chedoke Site; associate professor, McMaster University. Died Jan. 23, 2003, aged 55; survived by his wife, Fiona, and 2 children.