Letters
Correspondance

Interpreting the results of small trials

The randomized controlled trial of preventive home nursing visits for frail elderly people reported by Dawn Dalby and colleagues[1] raised several key issues regarding the design, interpretation and reporting of trials testing the efficacy of interventions in the elderly population.

With the testing of complicated interventions and the chronic shortage of resources in this area, clinical trials may be conducted with inadequate numbers of patients to reliably demonstrate positive effects. Dalby and colleagues enrolled 142 patients, giving the trial a prestudy power of 50%. Inadequate sample size will likely result in findings that have high statistical variability (low precision). Consequently, the 95% confidence intervals around the point estimates of the primary outcome for the control and intervention groups will be imprecise and are likely to overlap and result in statistically insignificant results. As the number of patients in the trial increases, the 95% confidence intervals become more precise with less overlap (if there is a positive treatment effect) and the results may become statistically significant. For these reasons, the study by Dalby and colleagues does not demonstrate that nursing visits are ineffective. In fact, no firm conclusions can be drawn from its results.

The authors cited their lack of adequate power as a possible explanation for their lack of statistically significant results. From a methodological and theoretical perspective, Goodman and Berlin[2] have argued against the use of post hoc power to explain negative trials. Once a trial is completed, they argue, the use of confidence intervals, rather the post hoc power, is the proper way to interpret trials with results that do not reach statistical significance.

The danger inherent in conducting small, inadequately powered trials is that potentially effective interventions will be judged as ineffective simply because of the inability to detect statistically significant and clinically important benefits. Consequently, caution must be exercised when embarking on small trials and interpreting the results.

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2. Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med* 1994;121:200-6.

Does the urea breath test tell us what we need to know?

The Feb. 8th issue of *CMAJ* had an interesting article by Carlo Fallone and colleagues concerning the urea breath test for *Helicobacter pylori* infection,[1] interesting not only for what the test will detect but for what tests it may push to the sidelines. There is certainly talk of the urea breath test lessening the need for gastroscopy, something that is welcomed as a means to cut costs and decrease patient discomfort and morbidity. But it does mean fewer chances to pick up premalignant lesions or early frank carcinoma. Protocols surrounding the urea test recommend scoping only when alarm signs appear, but clinical signs and symptoms are often the herald of higher stage disease. As a pathologist, all too often I see carcinoma cases from all parts of the GI tract presenting on the cutting table as advanced, node-positive disease.

It seems to me that at present we are not scanning, scoping or poking enough to detect the early, treatable malignancies. If our present diagnostic modalities are too expensive or risky for this more rigorous hunting, then surely more resources must be devoted to some sort of revolution in diagnostic imaging or direct visualization technology. Tasting and smelling for disease are no substitute for looking.

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Reference

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[The authors respond:]

The point Julius Wroblewski has brought up is a good one. We would certainly like to detect lesions early, rather than at a point when they are no longer treatable. However, we

must recognize that a definitive diagnosis is not necessarily required for adequate treatment and that serious diagnoses are rare in patients who present with gastrointestinal symptoms. We would also like to point out that the context for using the urea breath test in the "test and treat" approach for adult patients with dyspepsia is primary care.

Dyspepsia is extremely common, affecting 7% of patients presenting to a general practitioner's office, and it occurs with moderate severity in approximately 29% of Canadians.[1,2] It is obviously not feasible nor necessary for close to 30% of the Canadian population to undergo endoscopy. We should try to perform this procedure in the patients who would most benefit. In fact, if all patients with dyspepsia who present to a primary care physician were to have a gastroscopic examination the waiting list for this procedure would become enormous, potentially resulting in a delay in diagnosis for those patients with symptoms suggesting more significant pathology. Hence, we have to find ways to determine which patients may have significant pathology. Alarm features (vomiting, bleeding, anemia, abdominal mass, dysphagia and weight loss) and advanced age suggest a higher risk of pathology. Performing endoscopy on these individuals and simply performing a test for and treating *Helicobacter pylori* infection in those that do not have these risk factors may reduce the waiting lists for endoscopy and hence potentially increase the detection of early lesions.

Furthermore, once the urea breath test becomes more widely available, testing for and treating *H. pylori* infection would not result in a significant delay for further investigation if the patient were not to respond to treatment. A urea breath test result can be faxed within 24–48 hours and the course of treatment is only 1 week. In addition, a Canadian randomized controlled trial recently showed significant improvement in symptoms with the "test and treat" approach compared with placebo[3] and another study found this strategy to be significantly more cost-effective, without detrimental outcome, than a strategy using endoscopy first.[4]

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Submitting letters

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Distorted spending priorities in Canada

I was intrigued by a recent news item in *CMAJ* entitled "Detecting hep C for $1.5 million a case."[1] The title implies concern about the cost of a new program to identify donors infected with hepatitis C by nucleic acid amplification testing. I am concerned about any inference that the decision of the Canadian Blood Services to implement this program was cost-ineffective. I believe it would have been morally and fiscally irresponsible to decide otherwise.

If screening for hepatitis C were not introduced, all of the carriers detected would be denied vital personal information and possible treatment. Some could donate again and infect additional blood recipients. People who received the contaminated, unscreened blood products could potentially infect others. The lives of up to 13 Canadians every year could be ruined, with far-reaching effects on their family, friends and associates. The treatment, lost productivity, early disability and death of these 13 people would actually prove to be even more costly than the screening program.

Rather than focusing solely on the short-term cost-effectiveness of our underfunded health care system, let's look at the Canadian Blood Services' decision relative to the distorted priorities of our federal government. Consider, for example, the $30 million aid package recently offered to professional hockey franchises, the $3 million Ottawa spends on fireworks every Canada Day, the $2.4 billion of the $3 billion federal job creation program that our Auditor General says was wasted and the $5 billion spent on fruitless, politically motivated attempts to bail out defunct and poorly managed industries.[2]

We need to guard against pressures that could cause a return to the administratively and philosophically challenged processes that resulted in the demise of the Red Cross blood program — and a lot of Canadians. If we do not, the worst thing about the Canadian health care system could be that we deserve it.

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TB among aboriginal Canadians

The review by Mark FitzGerald and coworkers on the control of tuberculosis in aboriginal Canadians[1] would have been improved by a brief reference to the history of the disease among these first Canadians. Tuberculosis was recognized in aboriginal North Americans in the pre-Columbian period but only became a major problem in the latter part of the 19th century, after we and the Americans had destroyed their livelihood, impoverished them and crowded them together on reservations or in prison (as we still do).[2] Ferguson reported a mortality rate of 9000 per 100 000 in 1886, which is the highest rate ever recorded.[3] For treatment we sent aboriginal people to fill the beds of sanatoria in southern Canada, where many died. When their families came to see what had happened to them, even their graves couldn't be located.

In view of the increased incidence of tuberculosis in aboriginal populations, it is natural to consider preventive methods. Bacillus Calmette–Guérin vaccine has been administered to more than 3 billion people, but there remains considerable doubt that it accomplishes anything. In controlled studies the protective efficacy varies from 57% to more than 75%, and it is not clear that averaging such disparate results by meta-analysis is of any significance.[4] The efficacy is not, as the authors state, proven, and there is no reason to continue its wide use in aboriginal infants in contrast to the practice in the white population. Isoniazid prophylaxis in infected individuals is undoubtedly effective, but there has to be considerable caution in administering it to a population in which alcoholism and viral hepatitis are problems. The incidence of hepatotoxicity may be small, but the results can be catastrophic.[5,6] A better alternative to isoniazid might be a combination of rifampin and levofloxacin, with a minimal risk of hepatitis.

The authors worry, perhaps patronizingly, about the risks of "health transfer" — allowing aboriginal people to take over responsibility for their own health needs. Our record, at least where tuberculosis is concerned, is dismal. The best solution would be to facilitate the transfer process and provide aboriginal people with their own clinics, nurses and doctors.

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[The authors respond:]

We appreciate Leo Kahana's interest in our article on tuberculosis in aboriginal people in Canada.[1] He raises a number of important issues. We did not address the history of tuberculosis in Canada, as this subject had already been adequately covered by an earlier article in the *CMAJ* series on tuberculosis.[2] We indicated that the role of bacillus Calmette–Guérin vaccination in tuberculosis control is controversial. Kahana quotes reports showing a wide range of efficacy, but efficacy within Canada, which is most pertinent to our review, shows a significant benefit in case-controlled studies.[3] Many studies have shown underutilization of isoniazid chemoprophylaxis to be detrimental to tuberculosis control programs. The article by Mitchell and colleagues that Kahana cites refers to patients on active treatment;[4] one of us (J.M.F.) responded to this report with suggestions about a nonhepatoxic regimen.[5] There are no data on the combined use of rifampin and levofloxacin for chemoprophylaxis. Apart from toxicity, use of an expensive quinolone would incur significant additional costs. We are currently collaborating with the Tuberculosis Clinical Trials Consortium of the Centers for Disease Control and Prevention in Atlanta to develop a protocol to assess the efficacy of short-course chemoprophylaxis in non-HIV-infected people, which we hope will provide an alternative short-course regimen.

We disagree with Kahana's suggestion that we were patronizing in the section on health transfer. We welcome the concept of health transfer but caution that a public health surveillance system must remain in place. Our final conclusion was that tuberculosis control among aboriginal people must be "achieved in a culturally sensitive manner with a greater degree of community partnership that has been seen in the past." With this in mind, we are currently collaborating with the Institute of Health Promotion at the University of British Columbia to develop a community-based trainer program to involve First Nations people in planning and implementing community-driven and community-based chemoprophylaxis programs. By involving community members as well as health care professionals, it is hoped that we will be

able to achieve the aspiration that we all share: to reduce the unacceptable burden of tuberculosis among aboriginal people in Canada.

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Treating TB in the 1950s

CMAJ's recent review of tuberculosis[1–13] made me recall the way we used to treat tubercular meningitis, a particularly ugly illness in children. Before 1950, no children survived this dreadful disease — 3 weeks from onset and it was all over.

Courtesy of Nick Steinmetz

Fig. 1: The Alexandra Hospital in Montreal provided treatment for children with tuberculosis in the 1950s.

In 1950, I attended a lecture in Boston given by Dr. Honor Smith of Oxford University. Working with neurosurgeon Sir Hugh Cairns, he had treated children with tubercular meningitis successfully using a combination of purified protein derivative of the tubercle bacillus (PPD) and streptomycin, both intrathecally and intramuscularly.

While a resident in Boston, I had seen a number of children die because of tubercular meningitis. When I returned to Montreal later that year, my proposal to treat children who had tubercular meningitis with PPD for my "investigative year" in preparation for Royal College fellowship was accepted. By the end of 1951, 11 children had been treated, 9 of whom survived. The result was unprecedented, and this was probably the first group of children to have survived the disease in Canada or the United States.

This clinical effort took place at the Alexandra Hospital in Montreal (Fig. 1). Over the next 4 years, 100 children were treated, and 80% survived. During this time, 50 McGill interns provided devoted and enthusiastic care to these children.

The successful treatment had 2 results. First, the federal government made a substantial grant to the operation of the unit. Second, Dr. Jonathan Meakins, Sr., then professor of medicine at McGill, invited Quebec Premier Maurice Duplessis to visit the unit. After a sumptuous lunch in the dining room of the Alexandra Hospital — all lunches at the Alexandra were sumptuous and formal, with Dr. E.M. Worden carving — Meakins presented the premier with a 1-page report on the state of tuberculosis in Quebec; he compared it with the situation in Warsaw after WW II. Duplessis was shocked and deeply moved by the report, and the result was the immediate construction throughout Quebec of many hospitals to treat tuberculosis. Their wonderful impact is now history.

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Corrections to the *Compendium of Pharmaceuticals and Specialties*, 35th edition, 2000

This is to inform you of 2 corrections in the product recognition section of the 35th edition of the *Compendium of Pharmaceuticals and Specialties* (*CPS*).[1] On page R22, the photographs for Merck Frosst Canada & Co. products Singulair (montelukast sodium) 5 mg and Singulair (montelukast sodium) 10 mg were inverted. For further information, please refer to the product monograph for Singulair (montelukast sodium) on page 1464 of the *CPS*.

On page R10, the photograph of Bayer Inc. Consumer Care Division product Aspirin (ASA) 325 mg tablet was replaced by Aspirin (ASA) 325 mg caplet. For further information, please refer to the product monograph for Aspirin (ASA) on page 144 of the *CPS*.

We apologize for any inconvenience these errors may have caused our users.

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Reference
1. Canadian Pharmacists Association. *Compendium of Pharmaceuticals and Specialties*. 35th ed. Ottawa: The Association; 2000.