Canadian rotavirus vaccine effectiveness data

We read with interest and enjoyed Dr Goldman's recent Child Health Update on the effectiveness of rotavirus vaccines.[1]

In Australia, there are 4 states currently using the multiple-strain vaccine (ie, RV5), and the remaining 2 states and 2 territories are using the single-strain vaccine (ie, RV1).[2] Dr Goldman attributes our decline in rotavirus notifications and hospitalizations[3] to RV1, but in Queensland we have always used RV5.[4] Since mid-2007, we saw a rapid decline in rotavirus notifications in both vaccinated and older, unvaccinated age groups, and a fall in the proportion of laboratory tests positive for rotavirus in all age groups.[5]

Canada's experience with rotavirus vaccines provides a wonderful opportunity to observe the effects of rotavirus vaccines, particularly in indigenous children living in harsh arctic and subarctic regions. In the pre-vaccine era in Queensland, we found rotavirus disproportionately affected aboriginal and Torres Strait Islander children with higher rates of notification and hospitalization, and hospitalization earlier in life with a longer average length of stay.[6] Recent outbreak data from the Northern Territory, where RV1 has been used since late 2006, suggests effectiveness wanes rapidly after infancy in indigenous children.[7] To date, we have no equivalent data from a state that uses RV5, but we are collating these data in Queensland. Of note, middle-income Latin American countries have seen blunted effectiveness values, compared with efficacy data, with both vaccines.[8]

We look forward to Canadian effectiveness data, particularly from Canada's aboriginal population, as they become available to aid our understanding of rotavirus epidemiology in the vaccine era.

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Competing interests

Dr Lambert has previously been a co-investigator on clinical trials sponsored by Merck, CSL, and GlaxoSmithKline—manufacturers or distributors of rotavirus vaccines in Australia. Merck paid an honorarium to his institute for 2 rotavirus presentations to international meetings. **Dr Grimwood** has, in the past 10 years, been a member of a Rotavirus Advisory Board and received support for conference attendance, lecture fees, and a research grant from GlaxoSmithKline. He has also received a research grant from Merck.

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Canadian trial data?

The recent RxFiles by Kosar et al[1] is an excellent and helpful review of oral anticoagulant management in atrial fibrillation (AF). However, some serious questions arise when looking at the "unexpected" high hemorrhagic stroke rates in the warfarin arms of these trials (RELY [Randomized Evaluation of Long-term Anticoagulation Therapy], ROCKET-AF [Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in AF], and ARISTOTLE [Apixaban for Reduction in Stroke and Other ThromboembolLic Events in AF]), all of which were conducted multinationally with 39 to 45 countries participating, as opposed to a very low rate of hemorrhagic stroke experienced in the warfarin arm of the SPORTIF V (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation V) trial (2 events in 1962 patients), which was a North American–only trial of the first novel oral anticoagulant, ximelagatran. Perhaps it would be helpful if the Canadian data from these subsequent trials were published. Is the difference in hemorrhagic stroke rates owing to the change in settings of these studies from North America (the most relevant context for Canadian family physicians) to a multinational arena? What are the differences in the elements of the HAS-BLED score between these studies? What are the ranges of these elements as well?

It only takes a few outlier patients taking acetylsalicylic acid, with uncontrolled hypertension and poor warfarin control, to create large differences in bleed rates. Second, the hemorrhagic stroke issue aside, warfarin is demonstrated to be superior to dabigatran for all other major end points using RELY's own data when warfarin is managed properly and the average proportion of time the international normalized ratio is in therapeutic range is greater than 72.6%.[2] Why is so little attention paid to sensitivity analyses when discussing warfarin?

With simple and inexpensive computerized decision support tools, it is possible to achieve time in the therapeutic range of greater than 80%. I believe our most important problem has been poor warfarin management, not warfarin itself. Perhaps a few dollars spent on computerized support tools would be better value for money than the hundreds of millions being spent on switching to novel oral anticoagulants, with no method of monitoring the degree of anticoagulation (a substantial compliance issue), no effective antidote, and no long-term track record.

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Competing interests

Dr Trusler was the Chief of Staff of the Moose Factory General Hospital in Ontario where they employed 4S DAWN warfarin management software. This led to a dramatic improvement in the time in therapeutic range to greater than 80%. **Dr Niall Davidson** (neurologist) and **Dr Trusler** subsequently sourced and licensed a New Zealand product for Canada called INR Online. They hope to gain government sponsorship for the tool so that it can be available free to all Canadian family physicians to help them improve the time in therapeutic range for all of their patients taking warfarin. So far, they have had no revenue from this venture and a lot of expenses.

References

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Response

We appreciate the response from Dr Trusler regarding our article on oral anticoagulation in atrial fibrillation (AF).[1] He raises several interesting points. We are not aware of any publications extracting hemorrhagic stroke rates from ARISTOTLE, RELY, or ROCKET-AF by geographic location, nor what the differences in HAS-BLED risk criteria were at time of hemorrhagic stroke. We agree that the new oral anticoagulants likely have minimal to no advantage over well-controlled warfarin. We are aware of the subgroup analysis by Wallentin et al comparing the efficacy and safety of dabigatran to warfarin at different levels of international normalized ratio control.[2] It was reassuring to see that warfarin had similar outcomes to 150 mg of dabigatran twice daily when the mean time in the therapeutic range (TTR) was 65.5% to 72.6% (hazard ratio 0.69, 95% CI 0.44 to 1.09), and when mean TTR was greater than 72.6% (hazard ratio 0.95, 95% CI 0.61 to 1.48). As mentioned in our article, the Canadian Agency for Drugs and Technologies in Health recommends the use of new oral anticoagulants only in patients who are unable to achieve adequate anticoagulation with warfarin.[3] We also agree that there is need for better warfarin management.

The Canadian Agency for Drugs and Technologies in Health released a report on optimal warfarin management for the prevention of thromboembolic events in AF patients. The report included one study which examined TTR in AF patients; the TTR increased from 46% in 1992 using cardiologist-based manual dosing to 81% in 2006 using computer-assisted dosing in the same practice.[4] The report concluded by recommending a structured approach to warfarin therapy regardless of care setting. A computerized system for dosing warfarin might be a helpful tool; however, as Dr Trusler noted, not all centres can afford to incorporate one. An ideal structured approach for warfarin management would include ongoing patient education, follow-up, and dosing tools. Unfortunately, there likely is no one-size-fits-all solution owing to the variety of practice settings, provincial guidelines, local dosing nomograms, etc.

We appreciate the comments from Dr Trusler, which raise several interesting discussion points.

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