https://doi.org/10.14745/ccdr.v40i04a02

CATMAT *Statement on International Travellers and Typhoid* – a welcome development

Neumann I[1,2], Carrasco-Labra A[1,3] and Guyatt G[1*]

1. Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada
2. Department of Internal Medicine, School of Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile
3. Faculty of Dentistry, University of Chile, Santiago, Chile

* Corresponding author: guyatt@mcmaster.ca

An increasing number of organizations worldwide are updating their methods and standards to produce trustworthy clinical guidelines (1-6). In keeping with this welcome development, the Committee to Advise on Tropical Medicine and Travel (CATMAT) has used, for the first time, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to guideline development in its update of the *Statement on International Travellers and Typhoid* (7).

The merits of the GRADE approach include a highly structured, detailed, and transparent method for determining the appropriate level of confidence in estimates of intervention effects (8). Another key feature of the GRADE approach is the classification of recommendations as strong or weak. Strong recommendations should be applied to all or almost all the individuals in the relevant population and convey the message of "just do it". Weak (also called conditional) recommendations are sensitive to differences in peoples' values and preferences, and are therefore appropriate for most, but not all, relevant individuals. To determine the strength of the recommendation, guideline panels using the GRADE approach have to consider four factors: confidence in effect estimates, the balance between the benefits and harms, the end users' values and preferences, and – at least in some situations – resource utilization.

The updated CATMAT statement addresses one key clinical question: Should Canadian travellers use, or not use, typhoid vaccine? To address this question, CATMAT conducted a review of the evidence bearing on the impact of the available vaccines on the incidence of typhoid, and the associated morbidity and mortality. This is a well-framed clinical question that clearly and explicitly identifies the target population, the course of action under consideration, the relevant alternative, and the outcomes that are important to travellers.

The guideline authors conducted a systematic search and summarized the results of four randomized trials. They found no direct evidence regarding the effects of typhoid vaccination on morbidity and mortality, so the CATMAT recommendation was based on the effect of the vaccine on typhoid incidence.

In the GRADE approach, the evidence from randomized trials starts as "high confidence", but the confidence can be rated down if there are methodological limitations in the trials (risk of bias), imprecise or inconsistent results, systematic differences between the studied population and the target population (indirectness), or publication bias. One important limitation of the evidence available for the CATMAT statement was that the population included in the trials – people living in endemic areas – differed from the target population of the recommendation – Canadian travellers. Consequently, the CATMAT panel appropriately rated down the confidence from "high" to "moderate" because of indirectness.

The analysis conducted by the panel demonstrated that the use of typhoid vaccine versus no vaccine probably reduces the risk of clinical typhoid by ~50% (risk ratio 0.51; 95% confidence interval 0.42-0.62). However, given the low risk of typhoid in Canadian travellers (1/3,000 travellers for travel to South Asia; 1/50,000-100,000 for travel to Sub-Saharan Africa, North Africa and the Middle East, or South America; and < 1/300,000 for travel to the Caribbean and Central America), the absolute effect of typhoid vaccination is small to extremely small. On the

other hand, the absolute risk of adverse events is even smaller, and the burden of vaccination is probably not important for most travellers.

Finding no direct evidence regarding the preferences of travellers, the panel very commendably made its views about these preferences, and thus the threshold for vaccination, extremely explicit: the majority of Canadian travellers would consider the decrease in typhoid risk worth the cost and inconvenience of the vaccine if the absolute risk of typhoid were 1 in 10,000 or higher but not if the risk were less than this. Of the destinations considered, South Asia was the only region where the risk exceeded this threshold.

Failure to report explicitly the values and preferences used to develop the recommendation is the most common serious deficit in current practice guidelines. Very few panels make quantitative statements of the thresholds underlying their decisions. It is therefore highly commendable that the CATMAT panel did this.

Considering the confidence in effect estimates, the balance of benefits and harms, travellers' values and preferences, and the uncertainty regarding those preferences, the CATMAT panel issued two weak (conditional) recommendations: in favour of typhoid vaccine in Canadian travellers visiting South Asia but against its use in travellers visiting other destinations.

Compared with the previous statement produced 20 years ago, the updated CATMAT Statement on International Travellers and Typhoid reflects the major advances in the methods for developing clinical guidelines. Along with offering trustworthy recommendations regarding the use of typhoid vaccine in Canadian travellers, this work represents a model of how recommendations can be developed using the best available evidence with explicit acknowledgement of the importance of end users' values and preferences, and how they can be presented in a transparent and systematic way.

References

(1) World Health Organization. WHO handbook for guideline development. Geneva: World Health Organization (WHO), 2012.

(2) U.S. Preventive Services Task Force. Grade definitions (2012). Available at: http://www.uspreventiveservicestaskforce.org/

(3) Grading guide. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013.

(4) Guyatt GH, Norris SL, Schulman S, Hirsh J, Eckman MH, Akl EA, Crowther M, Vandvik PO, Eikelboom JW, McDonagh MS, Lewis SZ, Gutterman DD, Cook DJ, Schünemann HJ. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):53S-70S.

(5) Institute of Medicine. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, editor(s). Clinical practice guidelines we can trust. Washington (DC): National Academies Press; 2011. 2p.

(6) Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, Ventresca M, Brignardello-Petersen R, Laisaar KT, Kowalski S, Baldeh T, Zhang Y, Raid U, Neumann I, Norris SL, Thornton J, Harbour R, Treweek S, Guyatt G, Alonso-Coello P, Reinap M, Brozek J, Oxman A, Akl EA. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2013 Dec 16. [Epub ahead of print]

(7) Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011 Apr;64(4):380-2.

(8) Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6.