https://doi.org/10.14745/ccdr.v41i11a03

Advisory Committee Statement

Summary of the Committee to Advise on Tropical Medicine and Travel (CATMAT) Statement on Travellers' Diarrhea

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Abstract

Background: Most travellers' diarrhea (TD) infections occur during travel to low- and middle-income countries. Type of travel, duration of stay, age of traveller and presence of certain medical conditions are important factors to consider for risk of TD. The Committee to Advise on Tropical Medicine and Travel (CATMAT) assembled a TD working group to develop recommendations on prevention and treatment of TD in travellers. This document is a summary of the *Statement on Travellers' Diarrhea*.

Methods: Following a systematic review of the literature, recommendations on the prevention and treatment of TD were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate data quality, benefits and harms of the intervention, and values and preferences of the traveller. Other recommendations were based on a review of the literature and expert opinion.

Recommendations: Using the GRADE methodology, CATMAT concluded that oral cholera vaccine should not be routinely recommended to prevent TD in Canadian travellers. This recommendation was based on moderate quality data that showed this vaccine was not effective in preventing TD in travellers compared to placebo. Bismuth subsalicylate (BSS), fluoroquinolones or rifaximin are options for the prevention of TD based on high-quality data for BSS and fluoroquinolones and moderate evidence for rifaximin. For the treatment of TD, loperamide (alone or in combination with antibiotics), fluoroquinolones, azithromycin and rifaximin are all options, with varying degrees of data quality. Based on available evidence and expert opinion, CATMAT recommends handwashing or the use of hand sanitizer, as well as prudent choice and preparation of food and beverages as best practices for preventing diarrhea while travelling. At this time, a recommendation cannot be made for either the use of probiotics and prebiotics to prevent TD or the use of BSS to treat TD due to insufficient available evidence.

Conclusion: With the exception of BSS for prevention of TD (strong recommendation for use), CATMAT conditionally recommends the use of each of the other GRADE-evaluated preventive and therapeutic products assessed in this Statement. These CATMAT recommendations should be considered as options in the prevention and treatment of TD based on the particular situation of the traveller.

Preamble

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada with ongoing and timely medical, scientific, and public health advice relating to tropical infectious disease and health risks associated with international travel. The Agency acknowledges that the advice and recommendations set out in this Statement are based upon the best current available scientific knowledge and medical practices, and is disseminating this document for information purposes to both travellers and the medical community caring for travellers.

Persons administering or using drugs, vaccines or other products should also be aware of the contents of the product monograph(s) or other similarly approved standards or instructions for use. Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) or other

similarly approved standards or instructions for use by the licensed manufacturer(s). Manufacturers have sought approval and provided evidence as to the safety and efficacy of their products only when used in accordance with the product monographs or other similarly approved standards or instructions for use.

Introduction

Travellers' diarrhea (TD) is defined as the passage of three or more unformed stools in a 24-hour period, usually accompanied by one or more symptoms of varying degrees of severity, such as nausea, vomiting, abdominal cramps, fever or blood in stools (1). The most commonly identified causes of TD are the bacterial pathogens *Escherichia coli* (particularly *enterotoxigenic and enteroaggregative*) and *Campylobacter* (2). TD is mainly acquired through the ingestion of food and beverages contaminated with pathogens which cause diarrhea. Most TD infections occur during travel to low- and middle-income countries (3). Type of travel, duration of stay, age of traveller and presence of certain medical conditions are important risk factors to consider for TD (4).

Incidence rates for TD for those travelling up to two weeks in high-risk regions (low- and middle-income countries) range from 20% to 90% (1). Up to half of travellers with TD will experience some limitation of activities during their trip (5,6), while up to 10% may develop complications such as persistent diarrhea or post-infectious irritable bowel syndrome (7).

Options for the prevention of TD include hand hygiene, food and beverage precautions, probiotics, vaccination, and chemoprophylaxis. Treatment of TD involves use of antisecretory, antimotility and/or antibiotic agents. Rehydration is also an important aspect of managing TD, particularly for children.
The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada with ongoing and timely medical, scientific, and public health advice relating to tropical infectious disease and health risks associated with international travel. This is a summary of the CATMAT *Statement on Travellers' Diarrhea*; a full description of the evidence and recommendations is available (8).

Methods

This is the second CATMAT statement to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to develop recommendations. GRADE is a method of grading the quality of the evidence and strength of recommendations in guidelines used by many international organizations (9). This process stresses transparency and provides an explicit framework in which the following factors are considered and weighed when making recommendations: confidence in the estimate of effect (quality of data); balance of benefits and harms; and values and preferences. Resulting recommendations are expressed as strong or conditional. See **Table 1** for the GRADE recommendation categories, as well as the Appendix below for frequently asked questions on how to interpret GRADE results.

Table 1: GRADE recommendation categories

GRADE recommendation categories[1]	
Strong[2]: Recommendation FOR	The Committee believes that all or almost all well-informed people would want the recommended course of action and only a small number would not. ***Implication for practitioners:*** The balance of risks and benefits are such that most travellers would choose the intervention.
Strong[2]: Recommendation AGAINST	The Committee believes that all or almost all well-informed people would **not** want the recommended course of action and only a small number would. ***Implication for practitioners:*** The balance of risks and benefits are such that most travellers would **not** choose the intervention.

Conditional[3]: Recommendation FOR	The Committee believes that the majority of well-informed people would want the recommended course of action, but a minority (perhaps a large minority) would not. ***Implication for practitioners:*** With a conditional recommendation different travellers may make different choices. Practitioners should present the risks and benefits of the intervention and help each traveller make a decision consistent with his/her values and preferences.
Conditional[3]: Recommendation AGAINST	The Committee believes that the majority of well-informed people would **not** want the recommended course of action, but a minority (perhaps a large minority) would. ***Implication for practitioners:*** With a conditional recommendation different travellers may make different choices. Practitioners should present the risks and benefits of the intervention and help each traveller make a decision consistent with his/her values and preferences.

[1]Adapted from the GRADE handbook and GRADE guidelines, section 14 and 15 (9−11).
[2]The GRADE working group suggests that if a recommendation is "strong," then it is expected that 90% or more of informed individuals would choose (or not choose) the recommended course of action.
[3]The GRADE working group suggests that if a recommendation is "conditional," then it is expected that less than 90% of informed individuals would choose (or not choose) the recommended course of action.

Literature search and identification

An analytic framework identifying key interventions for prevention and treatment of TD was developed. Key questions to define the magnitude of benefits and harms were identified as well as key "Population of interest, Intervention, Comparison and Outcome" (PICO) questions. The following four questions were used to frame the GRADE assessment and recommendations:

- Among Canadian travellers, does the administration of the inactivated oral cholera vaccine (Dukoral®) decrease the risk of acquiring TD as compared to no vaccine (placebo)?
- Among Canadian travellers, does the administration of a relevant *chemoprophylactic* agent (i.e., antisecretory or antibiotic) decrease the risk of acquiring TD as compared to no chemoprophylaxis (placebo)?
- Among Canadians having acquired TD during travel, does the administration of a relevant *therapeutic* agent (i.e., antisecretory, antimotility, or antibiotic) decrease the duration and/or severity of TD as compared to *no therapy* (placebo)?
- Among Canadians having acquired TD during travel, does the administration of a relevant *therapeutic* agent (i.e., antisecretory, antimotility, or antibiotic) decrease the duration and/or severity of TD as compared to an *alternative therapy* (e.g., addition of antimotility to antibiotic, different class of antibiotic)?

Certain interventions were not amenable to a GRADE assessment, either due to a lack of valid evidence or credible alternative interventions to which a comparison could be made. Questions were also developed to frame these non-GRADE recommendations related to antimicrobial resistance patterns, hygiene, food and water precautions, use of probiotics, prebiotics and synbiotics, and management of TD-related dehydration in travellers.

Several electronic databases (Ovid MEDLINE, Embase, Global Health and Scopus) and the Cochrane Review Database were searched using variations on the term "travellers' diarrhea" and the relevant search term(s) for each intervention of interest. The search spanned the initial date for each database up to June 1, 2013. For all searches, only articles in English and/or French were retained. Reference lists from relevant studies were also scanned to identify any studies not captured by the database searches.

In our analysis, TD was defined as three or more unformed stools with at least one enteric symptom within a 24-hour period. Studies that used a less restrictive definition of TD were excluded for consistency in

diagnostic criteria and to ensure a selection of the evidence focused on symptoms that would be of importance to most travellers and practitioners. For studies evaluating antibiotics and vaccine, those conducted in a non-traveller population were excluded. For antisecretory and antimotility studies, non-traveller populations were considered in situations where traveller data were scarce, but their inclusion in the analysis led to a rating down in the overall quality of evidence.

Assessment of evidence

Full details on GRADE methodology are described elsewhere (12). Briefly, the GRADE approach rates the quality of the evidence for specific clinical outcomes across studies, not study by study, by addressing flaws in methodology, consistency and generalizability of results and demonstrated effectiveness of the intervention (13, 14). The GRADE approach takes into consideration the balance of benefits (efficacy) and harms of each TD preventive and therapeutic intervention, the confidence in the estimates of effect for each intervention (high, moderate, low, or very low), and what are believed to be the values and preferences of the traveller. GRADE quality assessments of study results, including the efficacy and adverse effects associated with each intervention, were collated into evidence profile and summary of findings tables (8).

Recommendations were expressed as strong or conditional, as previously described (15). Other recommendations did not use the GRADE approach and were based on evaluation of the relevant literature and expert opinion.

Results

Prevention of TD

Oral cholera vaccine

Dukoral® is licensed in Canada for prevention of and protection against TD and/or cholera in adults and children 2 years of age and older who will be visiting areas where there is a high risk of contracting TD caused by *Enterotoxigenic Escherichia coli (ETEC)* or cholera caused by *V. cholera.*

Moderate quality data showed the oral cholera vaccine (Dukoral®) (16) to be not effective in preventing TD in travellers compared to vaccination with placebo (relative risk (RR)=0.94; 95% confidence interval (CI)=0.82−1.09) (17−19). Overall, 35% of vaccinated subjects and 37% of non-vaccinated subjects developed diarrhea. A systematic review also demonstrated no significant difference in efficacy between this vaccine and placebo for prevention of TD (20). There are no reported harms of the vaccine and there are no data on patient preference.

Certain short-term travellers at high risk for health complications or serious inconvenience from TD may find that the potential benefits of the vaccine, based on their personal values and preferences, coupled with a low likelihood of adverse events, outweigh the burden of their risk. As such, the following travellers may still be considered for Dukoral® vaccination:

- those for whom a brief illness cannot be tolerated (i.e., elite athletes, some business or political travellers)
- those with increased susceptibility to TD (e.g., due to achlorhydia, gastrectomy, history of repeated severe travellers' diarrhea, young children >2 years)
- those who are immunosuppressed due to HIV infection with depressed CD4 count or other immunodeficiency states
- those with chronic illnesses for whom there is an increased risk of serious consequences from TD (e.g., chronic renal failure, congestive heart failure, insulin dependent diabetes mellitus, inflammatory bowel disease)

It should be noted that consideration of these groups is based on expert opinion and that there are no published data on Dukoral® use in these specific groups.

Bismuth subsalicylate (BSS)

High-quality data showed BSS to be effective in preventing TD in travellers compared to placebo (RR=0.55; 95% CI=0.44−0.67) (21−23). This strong effect was similarly found when restricted to those receiving a high or low dosage of BSS, and no difference in effect was found when comparing high to low dosage. There are no reported serious harms for BSS and there are no data on patient preferences.

Prolonged use of BSS in children carries a risk of salicylate intoxication and bismuth encephalopathy, as well as a theoretical risk of Reye's syndrome (24). Use of BSS is permitted in the case of certain children aged 2 years and older, based on an individual assessment of risks and benefits. BSS use is not recommended in children younger than 2 years of age.

Fluoroquinolones

High-quality data showed fluoroquinolones to be effective in preventing TD in travellers compared to placebo (RR=0.12; 95% CI=0.07−0.21) (25−28). A systematic review also demonstrated a significant protective effect for fluoroquinolones in preventing TD (29). However, fluoroquinolone use in non-traveller populations has been associated with serious adverse events such as cartilage damage, arthropathies, tendon rupture and *C. difficile*-associated diarrhea (30−33). Fluoroquinolone use in travellers is also associated with a potential risk of selecting for antimicrobial resistant pathogens (34−39). A relatively high percentage of travellers surveyed in the sole descriptive study on traveller values and preferences indicated a preference against taking antibiotics for prevention of TD (40).

Rifaximin

Moderate quality data showed rifaximin to be effective in preventing TD in travellers compared to placebo (RR=0.42; 95% CI=0.33−0.53) (41−45). The quality of the evidence was downgraded for potential publication bias due to the fact that results were unavailable for one large study registered on the U.S. government's clinical trials database. Two recent systematic reviews also found a significant protective effect for rifaximin in preventing TD (29,46). There are no reported harms for rifaximin use. Although no associations between rifaximin use in travellers and antimicrobial resistance have been documented, potential risks will need to be monitored.

Treatment of TD

Loperamide

Loperamide was found to be effective in reducing the duration and intensity of TD in travellers compared to placebo (e.g., RR for first relief from acute diarrhea after four hours of treatment = 1.69; 95% CI=1.17−2.45) (47−52). The estimate of effect was rated down for indirectness since studies in non-traveller populations were used. Confidence in the estimate of effect was also lowered for three of the four outcomes due to an insufficient number of study subjects (imprecision). There are no reported harms for loperamide use.

A small study suggests an increase in adverse events with the use of diphenoxylate (Lomotil, an agent related to loperamide) for treatment of shigella infection (53). Lomotil has a less favourable side effect profile, and it has not been studied in the treatment of TD.

Loperamide use in travelling children has not been studied. However, one randomized controlled trial conducted in children aged 2 to 11 years with acute diarrhea found that loperamide treatment significantly reduced duration and severity with no difference between loperamide and placebo treatment groups with respect to drug-related adverse events (54). Dosages differ by age group and treatment should not exceed two days. Loperamide should not be administered to children less than 2 years of age (24). A high proportion of North American travellers surveyed stated a preference for treatment with antidiarrheals including loperamide (40).

Loperamide in combination with antibiotics

The addition of loperamide to antibiotic therapy was found to be effective in reducing the duration of TD in travellers when compared to antibiotic use alone (e.g., RR for complete relief from TD after 24 hours = 1.55; 95% CI=1.28−1.86) (48,55,56). Estimates of effect for two of the four outcomes were rated down to due to substantial variation between studies in the observed direction of effect (inconsistency). There are no reported harms for using loperamide in conjunction with antibiotics. A high proportion of North American travellers surveyed stated a preference for treatment with antidiarrheals including loperamide and antibiotics. Given the relatively mild nature of most episodes of TD, and the acceptable efficacy of antibiotics or loperamide alone, it is reasonable to reserve the combination of the two for treatment of severe diarrhea and/or when treatment with either antimotility or antibiotic alone is unsuccessful.

Fluoroquinolones

Moderate quality data showed fluoroquinolones to be effective in reducing the duration of TD in travellers compared to placebo (RR for cure after 72 hours of treatment = 1.81; 95% CI=1.39−2.37) (57,58). The estimate of effect was rated down due to imprecision. Fluoroquinolone use in non-traveller populations has also been associated with certain serious adverse events and potential risk of selecting for antimicrobial resistant pathogens. Children under the age of 18 should not be administered fluoroquinolones for treating TD unless the benefits are felt to outweigh the potential risks and other alternatives are not feasible.

Azithromycin

Data comparing azithromycin directly to fluoroquinolones (specifically, ciprofloxacin and levofloxacin) showed that for four outcomes of interest, azithromycin had an equivalent or greater efficacy in reducing the duration of TD in travellers compared to fluoroquinolones (e.g., RR for recovery after 48 hours of treatment = 1.34; 95% CI=1.08−1.66) (59−62). For the outcome of rapid or immediate cure from TD, fluoroquinolones demonstrated a greater reported efficacy than azithromycin (RR=0.46; 95% CI=0.25−0.84) (59,61). These results suggest that azithromycin's ability to provide relief from TD is equivalent to that of fluoroquinolones. The data were assessed as being of low quality and were rated down due to various factors including: insufficient number of events for certain outcomes (imprecision); variability in results between each study (inconsistency); and differences between studies in terms of dosages and use of loperamide as an adjunct therapy (indirectness). The evidence does not appear to indicate any serious harm associated with use of azithromycin, although low-quality data from two studies demonstrated a higher risk for nausea immediately after treatment with azithromycin (RR=6.23; 95% CI=1.48−26.26) (61,62). Otherwise, there were no differences between the two therapies in other measures of nausea and vomiting.

Rifaximin

High-quality data showed rifaximin to be associated with a higher percentage of travellers cured of TD compared to placebo (RR=1.29; 95% CI=1.15−1.45) (63,64). High-quality data from two studies comparing rifaximin directly to fluoroquinolones (ciprofloxacin) showed there was no significant difference between rifaximin and fluoroquinolones with respect to proportion cured of TD (64,65). There were no reported harms for rifaximin use. Although no associations between rifaximin use in travellers and antimicrobial resistance have been documented, potential risks will need to be monitored.

Non-GRADE interventions

Recommendations were made for hand hygiene or food and water precautions without using the GRADE approach since these are non-invasive, low-impact preventive interventions with no credible alternative intervention to which comparisons could be made. Based on available evidence and expert opinion, CATMAT recommends washing of hands or use of hand sanitizer, as well as prudent choice and preparation of food and beverages as best practices for preventing diarrhea while travelling. At this time, a recommendation cannot be made for either the use of probiotics and prebiotics to prevent TD or the use of BSS to treat TD due to insufficient available evidence. A more detailed discussion of the available literature on these subjects can be found in the full TD Statement (8).

Recommendations and conclusions

With the exception of BSS for prevention of TD (strong recommendation for use), CATMAT conditionally recommends the use of each of the other GRADE-evaluated preventive and therapeutic products assessed in this Statement (see **Table 2**). These recommendations are conditional due to: demonstrated weak effects, weakness in the evidence base for a given intervention, and/or the uncertain weight which should be accorded to potential harms of the intervention.

One of the potential harms lies in the use of antibiotics which may select for carriage of resistant pathogens by the host. This in turn could lead to an ill traveller being treated for TD (or another infection) with ineffective antibiotics. Although this risk has been well-demonstrated in other domains, there is no reliable evidence on the presence or magnitude of the risk in the case of TD. CATMAT recommends that more systematic surveillance and research be undertaken on resistance patterns of pathogens in the returned traveller who has taken a course of antibiotics to prevent or treat TD. This information will improve assessment of baseline risk for resistance based on destination and type of travel.

Although CATMAT had moderate confidence in the available evidence to conditionally recommend against routine use of the oral cholera vaccine Dukoral® for prevention of TD, further research evaluating the efficacy of this vaccine to prevent TD would be necessary to make a more definitive recommendation for or against its use in specific populations.

Table 2: GRADE recommendations on the prevention and treatment of travellers' diarrhea for Canadian travellers

GRADE recommendations	
Prevention of travellers' diarrhea	
CATMAT suggests	• Oral cholera vaccine (Dukoral®) not be routinely administered to Canadian traveller ***Conditional recommendation, moderate confidence in estimate of effect versus placebo.*** • Bismuth subsalicylate (BSS) be considered as an option for adults at significant risk, and who are willing to accept multiple doses per day (2.1g−4.2g/day, divided into four doses per day). ***Strong recommendation, high confidence in estimate of effect versus placebo.*** • Lower dosage (1.05g/day) of BSS could be used in situations where a higher dosage is not feasible. ***Conditional recommendation, low confidence in estimate of effect versus placebo, low confidence there is no difference in effect between high and low dosage.*** • Fluoroquinolones be considered as an option in select high-risk short-term traveller populations where chemoprophylaxis is considered essential. ***Conditional recommendation, high confidence in estimate of effect versus placebo. Balance of benefits and harms based on available evidence on adverse events and antimicrobial resistance patterns.*** • Rifaximin be considered as an option. ***Conditional recommendation, moderate confidence in estimate of effect versus placebo. Balance of benefits and harms based on available evidence on antimicrobial resistance patterns.***

Treatment of travellers' diarrhea	
CATMAT suggests	• Loperamide be considered as an option. ***Conditional recommendation, low to moderate confidence in estimate of effect compared to placebo.*** • Fluoroquinolones be considered as an option. ***Conditional recommendation, moderate confidence in estimate of effect versus placebo. Balance of benefits and harms based on available evidence on adverse events and antimicrobial resistance patterns.*** • Use of loperamide in conjunction with antibiotic therapy be considered as an option. ***Conditional recommendation, moderate to high confidence in estimate of effect compared to antibiotic use alone.*** • Azithromycin be considered as an option. ***Conditional recommendation, low confidence in estimate of effect versus fluoroquinolone use. Balance of benefits and harms based on available evidence on antimicrobial resistance patterns and adverse events.*** • Rifaximin be considered as an option. ***Conditional recommendation, high confidence in estimate of effect versus placebo, moderate to high confidence in estimate of effect versus ciprofloxacin. Balance of benefits and harms based on available evidence on antimicrobial resistance patterns.***
"Best practice" recommendations for prevention of travellers' diarrhea	
CATMAT suggests	• Handwashing with soap and water before preparing meals, before eating meals, and after urination or defecation. • Alcohol-based hand sanitizers may aid in reducing the risk of diarrheal illness among travellers. • Consumption of undercooked or raw meats and seafood (66,67) and unpasteurized eggs and dairy products (66) are best avoided. Foods cooked earlier in the day and not sufficiently reheated are also best avoided (68). • Consumption of fruits and vegetables that are difficult to clean (e.g., broad-leafed vegetables), or peel (69), or foods that are prepared, stored or served in unsanitary conditions (70) are best avoided. • Moist food items served at room temperature are best avoided (71). Dry items such as bread and rolls are safer to consume (72). • Bottled carbonated and alcoholic drinks may be relatively safe to drink while travelling. • Non-carbonated bottled water with intact seals can generally be assumed to be safe to drink. • Bringing water to a boil is the most effective way of producing potable water. • Water filtration should be followed by chemical disinfection (73).

Acknowledgements

This summary was developed by the TD working group: M. Libman (Chair), Y. Bui, J. Geduld, P. McDonald, F. Reyes-Domingo, and C. Steensma.

CATMAT acknowledges and appreciates the contribution of Mona Abdel-Motagally to the development of the summary; and to Dr. Holger Schünemann, Professor and Chair, Department of Clinical Epidemiology and Biostatistics, McMaster University, GRADE in providing methodological support.

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Conflict of interest

None

Funding

This work was supported by the Public Health Agency of Canada.

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Appendix: Frequently asked questions on how to interpret GRADE results

Question: How is the confidence in estimate of effect measured?

Answer: In the GRADE approach, study results are pooled together by outcome and an estimate of effect is determined using meta-analysis techniques. The quality of this evidence is then assessed based on five criteria:

- Risk of bias (i.e., limitations in the design and/or execution of the study)
- Imprecision (e.g., insufficient number of study subjects to detect effect)
- Inconsistency (i.e., too much variability in results between each study)
- Indirectness (e.g., important differences in how the outcome or intervention were measured across studies)
- Potential publication bias (i.e., studies with no effect or undesired effect were not published and therefore cannot be assessed in the analysis)

For each individual criterion not met, one must rate down the quality one point on the four-point scale, ranging from "high" to "very low." In addition, the reasoning behind each downgrade must always be noted.

Question: Does the confidence in the estimate of effect directly define the strength of a recommendation?

Answer: No. The strength of the recommendation is not only based on the estimate of effect but it also takes into account the nature of the risks and benefits, and the related values and preferences of the traveller.

Question: What does a "conditional" recommendation mean in practice?

Answer: GRADE-based recommendations in this Statement labelled "conditional" mean that CATMAT believes that the majority of well-informed travellers would choose the recommended course of action; however, a minority (perhaps a large minority) would not. This is either because the benefit of the intervention in question is modest, the confidence in estimate of effect is not high, or there are serious considerations for potential harm. An example of potential harm in the case of antibiotic use for TD prevention and treatment is the presence of antimicrobial resistance patterns.

Question: If one was to conclude through the GRADE process that there was a high level of confidence in the estimate of effect for Intervention A and a moderate level of confidence in the estimate of effect for Intervention B, does that mean that Intervention A is better or more effective than Intervention B?

Answer: No. The fact that these interventions have separate assessments of quality of evidence means by definition that they are being indirectly compared. If, for example, Intervention A is compared to placebo and Intervention B is compared to placebo, we cannot infer that A is better than B since this is an indirect comparison.

If, on the other hand, we are evaluating studies making a direct comparison between each intervention, we may make an assessment of preference for one intervention over the other. However, this will still depend on a global assessment of the estimate of effect and quality of evidence for each outcome of interest, not to mention specific needs of special groups such as children, values and preferences of travellers, etc. For the TD Statement, the only direct comparisons made between interventions for treatment of TD are: loperamide and antibiotic vs. antibiotic alone; azithromycin vs. fluoroquinolones; and rifaximin vs. fluoroquinolones.

Question: Why is some of the evidence assessed using GRADE in this Statement while other evidence is not?

Answer: CATMAT concluded that certain interventions were not amenable to the GRADE approach, either due to lack of credible alternatives to the intervention in question (e.g., handwashing for the prevention of TD) or an insufficient evidence base (e.g., food and beverage choice for the prevention of TD, use of probiotics for the prevention of TD). As such, CATMAT provided recommendations for these interventions based on a review of the literature and expert opinion.