STATEMENT ON TRAVELLERS' DIARRHEA

AN ADVISORY COMMITTEE STATEMENT (ACS)

COMMITTEE TO ADVISE ON TROPICAL MEDICINE AND TRAVEL (CATMAT)

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

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Également disponible en français sous le titre :
Déclaration sur la Diarrhée du Voyageur

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Publication date: April 2015

Cat.: HP40-140/2015E-PDF
ISBN: 978-1-100-25905-5
Pub.: 140542

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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.

KEY POINTS/MESSAGES

The goal of this statement is to provide an updated clinical and epidemiological portrait of travellers' diarrhea (TD), including known risk factors, and to make recommendations on the use of various interventions for the prevention and treatment of TD.

TD is mainly acquired through the ingestion of food and beverages contaminated with pathogens which cause diarrhea. Globally, the most common causes of TD are the bacterial pathogens *Escherichia coli* (particularly, enterotoxigenic and enteroaggregative *Escherichia coli*) and *Campylobacter*, although there are important variations by region of travel. Most 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 risk factors to consider for TD.

Incidence rates for TD for those travelling up to two weeks in high risk regions (low and middle income countries) range from 20–90%. Although TD is usually a mild and self-limiting disease, up to half of travellers with TD will experience some limitation of activities during their trip while up to 10% will experience persistent diarrhea or other complications.

Where feasible and relevant, recommendations for the prevention and treatment of TD were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. GRADE considers the balance of benefits (efficacy) and harms of each intervention, including our confidence in the estimate of effect (high, moderate, low, very low), and what CATMAT believes to be the values and preferences of the traveller regarding prevention and treatment of TD. Please refer to the FAQ box below for more details on interpreting GRADE recommendations.

GRADE RECOMMENDATIONS

Prevention

1. CATMAT suggests that the oral cholera vaccine (killed whole cells plus recombinant B-subunit, WC-rBS, licenced for use in Canada as Dukoral®[1]) not be routinely administered to Canadian travellers as a means of preventing travellers' diarrhea (TD); **Conditional recommendation, moderate confidence in estimate of effect versus placebo.**
   - Moderate quality data showed the vaccine not to be effective in preventing TD in travellers compared to vaccination with placebo: relative risk (RR) = 0.94 (95% CI: 0.82 – 1.09). Overall 35% of vaccinated subjects and 37% of non-vaccinated subjects developed diarrhea. There are no reported harms of the vaccine and there are no data on patient preference. Given that there is no demonstrated benefit to the vaccine, CATMAT does not recommend routinely giving the vaccine to travellers.

2. CATMAT recommends that bismuth subsalicylate (BSS) be considered as an option for preventing TD for adults at significant risk, and who are willing to accept multiple doses per day (2.1–4.2g/day, divided in four doses per day); **Strong recommendation, high confidence in estimate of effect versus placebo.**

3. CATMAT suggests that a lower dosage (1.05g/day) of BSS could be used to prevent TD 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.**
   - High quality data showed BSS to be effective in preventing TD in travellers compared to placebo: RR = 0.55 (0.44 – 0.67), resulting in 250 fewer cases of TD per 1000 travellers treated. 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. However, low quality of data for the high and low dosage subgroups was observed. There are no reported serious harms for BSS and there are no data on patient preference.

4. CATMAT suggests that fluoroquinolones be considered as an option in the prevention of TD 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.**
   - High quality data showed fluoroquinolones to be effective in preventing TD in travellers compared to placebo: RR = 0.12 (0.07 – 0.21), resulting in 293 fewer cases of TD per 1000 travellers treated. However, although not documented in travellers, fluoroquinolone use in other populations has been associated with serious adverse events such as cartilage damage, arthropathies, tendon rupture and *C. difficile*-associated diarrhea. In addition, benefits may be less than anticipated due to increasing antibiotic

[1] Dukoral® is licensed for prevention of and protection against TD caused by ETEC and/or cholera caused by *V. cholerae*. However, research used to support this indication were not conducted within traveller populations.

resistance since these studies were performed. Fluoroquinolone use in travellers is also associated with a potential risk of selecting for antimicrobial resistant pathogens among endogenous flora. Finally, a relatively high percentage of travellers surveyed indicated they preferred not taking antibiotics for prevention of TD. For these reasons, CATMAT recommends that fluoroquinolone use for the prevention of TD be limited to certain selected short-term travellers at high risk for health complications or serious inconvenience from TD.

5. CATMAT suggests that rifaximin be considered as an option in the prevention of TD; **Conditional recommendation, moderate confidence in estimate of effect versus placebo. Balance of benefits and harms based on available evidence on antimicrobial resistance patterns.**
    - Moderate quality data showed rifaximin to be effective in preventing TD in travellers compared to placebo: RR = 0.42 (0.33 – 0.53), resulting in 213 fewer cases of TD per 1000 travellers treated. Although no associations between rifaximin use in travellers and antimicrobial resistance have been documented, potential risks will need to be monitored. There are no reported harms for rifaximin use. A relatively high percentage of travellers surveyed indicated they preferred not taking antibiotics for prevention of TD.

Treatment

6. CATMAT suggests that loperamide be considered as an option in the treatment of TD; **Conditional recommendation, low to moderate confidence in estimate of effect compared to placebo.**
    - Data ranging from low to moderate quality showed loperamide 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 4 hours of treatment = 1.69 (95% CI: 1.17 – 2.45), resulting in 145 more cases of rapid first relief per 1000 travellers treated. There are no reported harms for loperamide use. A high proportion of North American travellers surveyed stated a preference for treatment with antidiarrheals including loperamide.

7. CATMAT suggests that fluoroquinolones be considered as an option in the treatment of TD; **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.**
    - 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), resulting in 322 more cases of cure after 72 hours per 1000 travellers treated. Very low quality evidence showed fluoroquinolone use for treatment of TD to increase the risk of experiencing an adverse event (most commonly headaches, constipation, nausea and fatigue). Fluoroquinolone use in non-traveller populations has also been associated with serious adverse events such as cartilage damage, arthropathies, tendon rupture and *C. difficile*-associated diarrhea. Their use in travellers

is associated with a potential risk of selecting for antimicrobial resistant pathogens. A high proportion of North American travellers surveyed stated a preference for treatment with antidiarrheals including antibiotics.

8. CATMAT suggests that the use of loperamide in conjunction with antibiotic therapy be considered as an option in the treatment of TD; **Conditional recommendation, moderate to high confidence in estimate of effect compared to antibiotic use alone.**
   - Data ranging from moderate to high quality showed the addition of loperamide to antibiotic therapy 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), resulting in 200 more cases of complete relief after 24 hours per 1000 travellers treated with adjunct loperamide. 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.

9. CATMAT suggests that azithromycin be considered as an option in the treatment of TD; **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.**
   - Low quality data comparing azithromycin directly to fluoroquinolones showed azithromycin to be equally or more effective 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), resulting in 134 more cases of recovery after 48 hours per 1000 travellers treated with azithromycin over fluoroquinolones. The exception is in rapid or immediate cure from TD, where fluroquinolones had greater reported efficacy than azithromycin: RR = 0.46 (95% CI: 0.25 – 0.84). Taken together, these results suggest that azithromycin's ability to provide relief from TD is equivalent to that of fluoroquinolones. Although the evidence is less conclusive than for fluoroquinolones, azithromycin use does pose a potential risk of selecting for antimicrobial resistant pathogens. The evidence does not appear to indicate any serious harm associated with use of azithromycin, although low quality data demonstrated a higher risk for nausea immediately after treatment with azithromycin: RR = 6.23 (95% CI: 1.48 – 26.26), resulting in 68 more travellers with nausea in the first 30 minutes of treatment per 1000 treated with azithromycin as compared to those treated with fluoroquinolones. Otherwise, there were no differences between the two therapies in other measures of nausea and vomiting. A high proportion of North American travellers surveyed stated a preference for treatment with antidiarrheals including antibiotics.

10. CATMAT suggests that rifaximin be considered as an option in the treatment of TD for travellers; **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.**
    - 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), resulting in 177 more travellers cured of TD at the end of follow-up per 1000 treated. High quality data comparing rifaximin directly to fluoroquinolones (ciprofloxacin) showed there was no significant difference between rifaximin and fluoroquinolones with respect to proportion cured of TD (RR=0.98, 95% CI: 0.90 – 1.07). Although no associations between rifaximin use in travellers and antimicrobial resistance have been documented, potential risks will need to be monitored. There are no reported harms for rifaximin use. A high proportion of North American travellers surveyed stated a preference for treatment with antidiarrheals including antibiotics.

GRADE recommendations were not made for hand and food hygiene since they are non-invasive, low impact interventions with no credible alternative intervention to which comparisons could be made. Nevertheless, 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 GRADE recommendation cannot be made for the use of probiotics and prebiotics to prevent TD nor the use of BSS to treat TD due to insufficient available evidence.

It should be noted that, due to the scarcity of evidence on TD prevention and treatment in children, caution should be used when extrapolating any of the recommendations in this document to children, unless specifically mentioned.

BOX 1: 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); and 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 a re: loperamide and antibiotic vs. antibiotic alone for the treatment of TD; azithromycin vs. fluoroquinolones for the treatment of TD; and rifaximin vs. fluoroquinolones for the treatment of TD.

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., hand washing 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 solely on a review of the literature and expert opinion.

INTRODUCTION

Diarrhea is a common medical problem affecting travellers, especially those who travel to low and middle income countries where there is a higher risk of encountering suboptimal sanitation and hygiene conditions (1). Travellers' diarrhea (TD) can adversely affect travel plans and incur financial costs to the traveller, especially if medical care is required while travelling. Several factors, both travel-related (i.e. destination and type of travel) and traveller-related (i.e. country of origin, age) affect the risk of acquiring diarrhea (2) and the severity of symptoms.

The purpose of this statement is to provide health care professionals with information on risk factors, and recommendations for the prevention and treatment of TD. Information specifically addressing persistent diarrhea in the returned traveller is included in a separate statement (3).

BACKGROUND

CLINICAL AND EPIDEMIOLOGICAL FEATURES

Symptoms of TD range from mild to severe. Classical TD is defined as the passage of three or more unformed stools in a 24 hour period with at least one accompanying symptom including: nausea, vomiting, abdominal cramps or pain, fever or blood in stools (dysentery) (4).

Symptoms of TD in adults tend to occur early during the trip, with onset dates reported on average during the third or fourth day of travel (5, 6). However, children and youth under the age of 20 have been reported to experience a later average onset at eight days (7). The duration of TD generally averaged between three to four days among adult travellers (5, 6), although average duration of incapacitation (i.e. unable to pursue planned activities) due to TD did not exceed 30 hours (5, 6, 8). Longer durations of TD were observed in children, particularly those two years of age and younger (7). Between 2 to10% of travellers may develop persistent diarrhea (i.e. lasting two weeks or longer) (9).

Although TD is usually a mild and self-limiting disease, between 5% to 20% of travellers sought professional help (i.e. consulted a physician, nurse or pharmacist), between 30% to 60% used some form of medication, and some individuals required hospitalization (5–7). In addition, between 12% to 50% of travellers were incapacitated for part of the trip due to TD (5, 6) and 5% to10% may develop post-infectious irritable bowel syndrome (PI-IBS)(9).

ETIOLOGICAL AGENTS

TD is mainly acquired through the ingestion of food and beverages contaminated with pathogens that cause diarrhea. The most common etiologic agents for TD are bacterial, viral and parasitic. Bacterial pathogens, particularly enterotoxigenic and enteroaggregative *Escherichia coli* (ETEC and EAEC respectively) and *Campylobacter*, are the most common. A review of 51 studies on TD (10) found that roughly one third of TD cases from Latin America, the Caribbean, Africa, and South Asia were due to ETEC and one third of the cases from Southeast Asia were due to *Campylobacter*. Other bacterial pathogens such as *Shigella* and *Salmonella* accounted for a combined 10% to 15% of TD cases in those regions. *Aeromonas*

and *Plesiomonas* species were more commonly reported in Asia and Africa and accounted for 5% to 8% of TD cases in those regions, while *Vibrios* accounted for 9% of the cases in Southeast Asia.

The most common viral pathogens that cause TD are noroviruses and rotaviruses which accounted for 19% to 25% of TD cases in Latin America, the Caribbean and Africa and between 3% to 5% of TD cases in Asia (10). Noroviruses were also implicated in many gastrointestinal outbreaks on cruise ships (11).

Parasitic pathogens such as *Giardia*, *Cryptosporidium* and *Entamoeba histolytica*, accounted for 2% or less of TD cases from Latin America, the Caribbean and Africa and between 8% to12% of cases in Asia (10). *Cyclospora cayetanensis* has also caused diarrhea in travellers returning from Latin America, the Indian sub-continent and Southeast Asia (12). Although parasitic pathogens are responsible for a smaller proportion of TD cases globally, diarrhea due to parasites tends to be more protracted and, consequently, requires health care intervention more frequently upon return from travel. Among travellers who visited a GeoSentinel travel clinic[2] to seek post-travel medical care, parasitic pathogens represents the most frequently identified cause of acute diarrhea (13). Diarrhea due to *Giardia* and other gastrointestinal parasites were also reported more frequently in long-term travellers seeking post-travel medical care than short-term travellers (14).

In the review article noted above (10), no etiologic agent could be identified for approximately 40% to 50% of TD cases despite thorough microbiological evaluation. However, there is evidence to suggest that bacterial pathogens are responsible for many of these pathogen-negative TD cases as there are many documented cases of symptoms being reduced through use of antibacterials. Two studies using more sensitive laboratory methods for detecting pathogens such as PCR demonstrated that ETEC, EAEC and diffusely adherent *Escherichia coli* (DAEC) accounted for 26% to 30% of TD cases originally characterized as pathogen negative in travellers to Guatemala, Mexico, Jamaica and India (15, 16).

EPIDEMIOLOGY

A review of data from observational studies of diarrhea rates among travellers originating from high income countries found that incidence rates for two-week stays ranged from 20% to 90% for travel to high-risk regions (low and middle income countries) (4). Between 55% to 59% of ill returned travellers who visited one of the travel clinics associated with GeoSentinel were diagnosed with acute diarrhea (1). A study of travellers visiting four high-risk countries conducted in the late 1970s and again in the late 1990s found that TD rates remained similar over this 20 year time period (6, 17). However, a subsequent study in one of these four countries has shown a decline in rates of TD since the late 1990s which is thought to be due to efforts for improved hygiene in tourist facilities (18).

[2] GeoSentinel travel clinics are a worldwide communication and data collection network of 54 globally dispersed travel and tropical medicine clinics.

Preliminary findings from C-EnterNet, an integrated enteric pathogen surveillance system with two sentinel sites in Canada (Ontario and British Columbia), for the 2011 surveillance year indicated that 30% of all cases of reportable enteric disease in Canada were associated with international travel (19). There have been regional variations reported, with 25% in Waterloo, Ontario (from June 2005 to May 2009) (20) and 40% reported in British Columbia (in 2008) (21). In the study from Waterloo, the travel-related cases accounted for 18% of the hospitalizations for enteric illness reported during that study period (20). Note that the studies conducted through C-EnterNet only target reportable illnesses such as campylobacter enteritis, salmonellosis and giardiasis and therefore do not include other more notable travel-related etiologies for diarrhea such as enterotoxigenic *Escherichia coli*. Hence, the findings above only represent a fraction of all travel-related cases of diarrhea in Canada.

METHODS

This statement was developed by a working group comprised of volunteers from the CATMAT committee, none of whom declared a relevant conflict of interest. All working group members were approved by the CATMAT secretariat and chair. The working group, with support from the secretariat, was responsible for: literature retrieval, synthesis and analysis; and the development of key questions and draft recommendations. The final statement was approved by the full CATMAT membership.

Recommendations in this statement on interventions to prevent and treat TD were developed using the GRADE methodology, wherever relevant and feasible. This approach has been increasingly adopted by guideline developers (22, 23). It stresses transparency and provides an explicit framework in which the following factors are considered and weighed when making a recommendation(s): confidence in the estimate of effect (quality of data, see Box 1: FAQ on pg. 6 for details); balance of benefits and harms; and values and preferences. Resulting recommendations are expressed as strong or conditional (see Box 1: FAQ on pg. 6 for details).

Various recommendations for preventive and treatment interventions provided within this statement include off-label use of medications. Product monographs or other similarly approved standards or instructions for use should be reviewed prior to use.

The following summarizes the process used to develop this statement:

For the GRADE recommendations:

1. The following key "PICO" (population of interest, intervention, comparison and outcome) questions were identified:
    a. 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)?
    b. 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)?

c. 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)?

d. 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)?

2. Key questions to define the magnitude of benefits and harms were also identified:
   a. What harms are associated with TD chemoprophylactic and therapeutic agents, as well as with vaccination?
   b. What are the important risk factors for TD among travellers (e.g., destination, duration of travel, age, comorbidities such as infection with HIV or acid suppression/achlorhydria)?
   c. What are the values and preferences of travellers regarding the magnitude of risk reduction in TD that would make use of the relevant intervention worthwhile given the associated cost and inconvenience?

3. With the aid of a reference librarian, a strategy was developed to identify relevant literature. 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 or terms 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. See Appendix 1 for an example of a search strategy used. Reference lists from relevant studies were also scanned to identify any studies not captured by the database searches.
4. From these searches, literature addressing the population of interest, intervention, comparison and outcome ("PICO") and other questions was identified. Systematic reviews that addressed the efficacy and safety of the TD interventions were specifically sought out.
5. Although some studies evaluated prevention and treatment of mild or moderate TD, our recommendations only addressed outcomes using the classical definition of TD: three or more unformed stools with at least one enteric symptom within a 24 hour period. For studies evaluating antibiotics and vaccine, those conducted in a non-traveller population were also 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. Finally, several studies were excluded that evaluated antibiotics which are either no longer available in Canada or are no longer prescribed for TD due to widespread antibiotic resistance.
6. A quality assessment of studies evaluating the efficacy of each of the TD interventions was performed, and results were collated into evidence profiles and summary of findings tables (see Appendix 2) as per the GRADE methodology (24–26).

7. Recommendations were developed for use of each TD intervention, taking into consideration: a) our confidence in the estimates of the efficacy and harms of each intervention, b) the balance of harms and benefits, and c) the values and preferences of travellers. The cost of each intervention, normally borne by the traveller, was not explicitly considered as there were no data available on willingness to pay (WTP) for TD in travellers.

For the evaluation of interventions not given a GRADE recommendation:

8. The evaluation of certain interventions is not amenable to the GRADE approach, either due to lack of credible alternatives to the intervention in question (i.e., best practices considered as "common sense" approaches) or an insufficient evidence base. As such, CATMAT provided recommendations for these interventions based on a review of the literature, as well as expert opinion. The additional non-GRADE questions that were considered are the following:
    a. What are the documented antimicrobial resistance patterns for each of the antibiotics recommended for use in prevention and treatment of TD; and does pathogen susceptibility to antimicrobial treatment vary by destination?
    b. Do hygiene and/or food and water precautions reduce the risk of acquiring TD among travellers?
    c. Does use of probiotics, prebiotics, or a combination of the two (synbiotics) reduce the risk of acquiring TD among travellers?
    d. What are the best practices associated with managing TD-related dehydration among travellers?

RESULTS

RISK FACTORS

The following travel-related and traveller-related factors have been shown to affect the risk of acquiring TD or influence the type or severity of symptoms of TD.

Travel-related

Travel destination has a large influence on the risk of acquiring TD (1, 6). In a global retrospective observational analysis of gastrointestinal infection among illreturned travellers who visited a GeoSentinel clinic, travel to sub-Saharan Africa, South America or South Asia was associated with the highest reporting rate ratios (RRRs), which ranged from 203 to 890 (reference group: Northern and Western Europe); travel to Oceania, the Middle East, North Africa, Central America, the Caribbean or Southeast Asia was associated with lower reporting rate ratios (RRRs from 41 to 104); and travel to south/central/eastern Europe, North America, Northeast Asia or Australasia was associated with the lowest reporting rate ratios (RRRs from 2 to 17) (1). Rates also varied between countries within the same region: for example, within North America,

reporting rates were highest in Mexico and within Southeast Asia, reporting rates were lowest in Malaysia and Singapore (1). Among the Canadian GeoSentinel sites, approximately 30% of TD cases acquired their illness in the Caribbean and Central America (including Mexico), followed by South Central Asia and sub-Saharan Africa (18% each), Southeast Asia and South America (7% each), and 20% from other regions (27).

The type of travel and accommodation can also influence the risk of acquiring TD. The TD attack rates were higher among backpackers or travellers participating in adventure tours (i.e. staying in private accommodations, camps, cheap hotels or similar places) compared to those on a beach vacation (i.e. stay in one hotel along the shore) (17, 28). In addition, business travellers had a lower risk for TD compared to tourists and honeymooners (5, 6). A few studies have shown that staying in luxury accommodations compared to standard hotels does not necessarily reduce the risk of acquiring TD (17, 28).

The incidence of TD has been reported to increase with increased duration of stay of up to two to three weeks (5, 28, 29). Long-term travellers (trip duration more than 6 months) were more likely to have chronic diarrhea, giardiasis and post-infectious irritable bowel syndrome than short-term travellers (trip duration less than one month), while acute diarrhea and acute bacterial diarrhea were more common in short-term travellers (14).

Seasonality of travel appears to influence the risk of TD. In one study, Austrians who travelled to various regions in Africa, Asia, and in Central and South America had lower incidence rates for TD overall when they travelled during the months of December to March (typically colder months) than those who travelled during the months of June to September (typically warmer months) (28).

Traveller-related

Age of the traveller may affect the risk of TD. Younger adults (aged 30 years or younger) have been shown to be at highest risk for TD compared to older adults (5, 6, 28). In one observational study, children (<18 years of age) had a non-significant morbidity risk increase due to acute diarrhea compared to adults (adjusted for gender, travel region, reason for travel and travel duration), however younger children (≤11 years) had a significantly higher rate compared to older children (30). Another study also showed that small children (≤2 years) tended to have a more severe and prolonged clinical course for TD compared to other pediatric age groups (7).

Travellers who originated from high or intermediate risk regions for TD (i.e. South Asia and sub-Saharan Africa) had lower rates for TD compared to travellers who originated from low risk regions (i.e. North America and Australasia) (5, 31). Lower rates were also observed among travellers who reported recent (5, 6) or prior (17, 32) travel to the tropics or other low and middle income countries. Lower rates of TD were also reported in individuals who had experienced TD in the preceding year (33).

Some studies have shown that individuals may have a genetic susceptibility to certain etiologic agents for TD (34–36). Other pathophysiologic factors were also shown in several studies to influence the risk of diarrhea (i.e. diarrhea in HIV-infected individuals was found to be strongly associated with low CD4 cell counts (37); use of medication that reduces gastric acid secretion, such as proton pump inhibitors (38) and histamine 2 antagonists (39), increases susceptibility to bacterial infections such as *Campylobacter* and *Salmonella*). In the case of proton pump inhibitors however, the magnitude of the enhanced susceptibility to acute diarrhea from chronic use is not clear (38).

PREVENTION—BEST PRACTICES

Evidence regarding various "common sense" interventions thought to prevent TD was reviewed, including hand hygiene, food and beverage selection and water purification. As these are non-invasive interventions with broad applicability, they were not subject to a GRADE evaluation.

Hand Hygiene

The evidence for the effectiveness of hand hygiene (i.e. washing hands with soap and water or disinfection through the use of alcohol-based hand sanitizers) in preventing diarrhea in travellers is limited. Furthermore, hand hygiene would not be expected to prevent illness related to the consumption of contaminated food and water. Nevertheless, the importance of hand hygiene in reducing the risk of diarrheal illness among non-travel-related cases in both low to middle income (40–42) and high income (43, 44) countries has been well-documented. Findings from a systematic review conducted on the benefits of hand washing found that interventions that promote hand washing can reduce diarrheal episodes by about one-third (45). Therefore, hand washing with soap and water is recommended before preparing meals, before eating meals, and after urination or defecation.

Alcohol-based hand sanitizers are also becoming a more commonly used source of hand hygiene. A few studies found that hand rubbing with an alcohol-based solution was comparable to (46), or better than (47–49), hand washing with an antiseptic soap at reducing bacterial hand contamination. Therefore in the absence of ready access to soap and water, alcohol-based hand sanitizers may aid in reducing the risk of diarrheal illness among travellers.

Food and Beverage Selection

The ingestion of contaminated foods and beverages is an important risk factor for acquiring enteric pathogens associated with TD. The presence of these pathogens in food and beverage samples taken from higher risk travel destinations (50–52), as well as association of their consumption with travel-related enteric outbreaks (53) has been identified. An informal review of the literature (54) failed to find a correlation between practicing standard dietary precautions and the risk of acquiring TD. These studies, however, were mostly based on retrospective surveys prone to recall bias, as well as low response rates, and failed to take into account important modifying factors such as host immunity, age and location where meals are prepared. For example, preparing one's own food likely improves the level of food hygiene and has been shown to significantly lower the risk of developing TD (50).

Notwithstanding this lack of evidence, and in spite of some studies showing low compliance among travellers in following recommended dietary precautions (55, 56), travellers may still benefit from exercising caution in the choice of food and beverage consumption while travelling to higher risk areas as outlined below:

ADEQUATELY HEATED OR PASTEURIZED FOODS AND BEVERAGES

Temperatures above 65°C have been found to reliably kill all bacterial pathogens, thereby making consumption of foods and beverages that are served steaming hot (57) a lower risk option. Consumption of undercooked or raw meats and seafood (53, 58) and unpasteurized eggs and dairy products (53) have been implicated in the risk for TD and are best avoided. Foods cooked earlier in the day and not sufficiently reheated are also best avoided (59).

FOODS THAT ARE THOROUGHLY CLEANED AND STORED IN HYGIENIC CONDITIONS

Foods, particularly fruits and vegetables, which are not cooked or heated should be washed thoroughly in clean water or peeled prior to consumption to remove enteropathogens from the food surface. For travellers unable to prepare their own food, it is best to avoid fruits and vegetables that are difficult to clean (e.g., broad leafed vegetables) or peel (60), or foods that are prepared, stored or served in unsanitary conditions (61).

Soaking fruits and vegetables in disinfectants such as dilute bleach or permanganate solutions has been shown to reduce contamination. However, concentrations and contact time have not been well studied, and protozoal cysts will generally be resistant to relatively brief and incomplete contact. In addition, bleach loses its disinfectant properties in the presence of many organic compounds (62).

FOODS WITH LOW WATER AND HIGH SUGAR CONTENT

Bacteria need moisture for growth therefore moist food items served at room temperature are best avoided (63). Dry items such as bread and rolls would be safer to consume (64). However, the high sugar content in certain moist foods such as syrups, jellies, jams and honey inhibit the growth of bacteria and are assumed to be safe (63).

BOTTLED CARBONATED AND ALCOHOLIC DRINKS

An *in vitro* study of survival of several TD-related enteric pathogens in beverages (65) found that these pathogens were killed most quickly in wine, followed by carbonated drinks and beer. Greatest pathogen growth was observed in non-chlorinated drinking water and milk. Therefore bottled carbonated and alcoholic drinks may be relatively safe to drink while travelling.

ICE AND BOTTLED WATER

Ice made from purified water should be safe to consume; however, ice served at restaurants or by vendors may have been made from contaminated water sources and thus may not be safe (66). Several studies found the bacteriological quality of various brands of bottled water sold in several international destinations to be highly variable, and some judged to be unsatisfactory by accepted health standards (51, 67–69). Studies conducted in two higher risk countries found that all imported brands of bottled water tested were within the World Health Organization (WHO) standards for purity while some domestic brands were not (70, 71). However, non-carbonated bottled water with intact seals can generally be assumed to be safe to drink.

Water Purification

Purified water is safe to drink. Water purification while travelling may be achieved through heat, chemical disinfection (combined with filtration if possible) or through ultraviolet (UV) radiation. Bringing water to a boil is the most effective way of producing potable water because all common enteric pathogens are readily inactivated or killed by heat upon boiling, even at moderately high altitudes (72, 73). Water should be boiled for one minute or kept covered once boiled for slow cooling (73). Small portable heating coils or a kettle with an electrical outlet and current flexibility are inexpensive ways to ensure a constant supply of purified water.

Filters that trap particles of at least 0.2µm in size are effective against most bacteria and parasites; however most filters are not reliable for removal of viruses (73). Therefore if possible, water filtration should be followed by chemical disinfection (74).

Chemical disinfection may be achieved through the addition of a halogen such as iodine or chlorine to the water. Iodine, available in tablet form and in low concentrations, is effective in killing bacterial, viral and protozoal (except *Cryptosporidium*) pathogens (73, 75). Iodine is contraindicated in pregnant women and those with thyroid disease (74) and its use should be limited to periods of one month or less (73).

Chlorine is available in a variety of formulations, both tablet and liquid, including simple household bleach and commercial preparations of chlorine dioxide. Each form releases free chlorine in water that effectively kills many enteric pathogens depending on concentration and contact time (72). Halogen treated water may often be unpalatable. However, the taste can be improved by reducing the halogen concentration and increasing contact time proportionately. Alternatively, halogen treated water can be run through a filter that contains activated carbon or ascorbic acid crystals can be added after the required contact time has been achieved (62). Water purified by methods which do not have residual disinfecting activity can become recontaminated during storage. Halogens have prolonged activity, and in higher concentrations, allows water to be stored safely for prolonged periods.

UV pens emit rays that can kill bacteria, viruses, protozoa and other parasites in clear water; however, they can be costly compared to other water purification methods and they do not work in turbid conditions (cloudy water) (74). Solar water disinfection (SODIS) combines the effect of thermal heating of solar light with UV radiation to eliminate pathogens (76). However, this method may not be practical for most travellers due to the time required to disinfect the water: up to 48 hours of solar exposure, depending on the intensity of sunlight available as well as the sensitivity of the pathogens.

The choice of water purification method will vary according to the traveller's itinerary and personal preferences. Long-term travellers may prefer to boil their water throughout their travels as filters have finite life-spans and chemically-treated water is often unpalatable. Most short-term travellers on business trips or resort holidays may prefer limiting themselves to commercially bottled beverages while campers may prefer portable water filters possibly combined with halogen treatment.

PREVENTION—INTERVENTIONS

Probiotics, prebiotics and synbiotics

Due to various limitations explained below, CATMAT was unable to make a GRADE recommendation on the use of probiotics, prebiotics and synbiotics in the prevention of TD. An informal evaluation of the evidence is provided below.

Probiotics are live microbial food ingredients (i.e. certain types of living bacteria or yeast) that, when ingested in sufficient quantities, provide health benefits to the consumer (77). Prebiotics are non-digestable food ingredients (i.e., certain types of dietary fiber) which provide health benefits by selectively stimulating growth of certain bacteria in the colon (78). Synbiotics are products containing both probiotics and prebiotics. In Canada, probiotics, prebiotics and synbiotics are classified as natural health products (NHP) and, if reviewed by Health Canada, will be assigned a Natural Product Number (NPN) which is displayed on the product container. The Canadian regulations governing NHP are separate from the regulations governing prescription drugs. The more serious the health claim being made on the label, the higher the required level of evidence.

Several meta-analyses and reviews have evaluated the clinical effectiveness of probiotics in the prevention or treatment of symptoms for a variety of gastrointestinal diseases, such as lactose intolerance, irritable bowel syndrome, antibiotic-associated diarrhea, and those due to *Helicobacter pylori* and *Clostridium difficile* infections (77, 79–81). However, only a few randomized controlled studies have examined the use of probiotics in the prevention of TD with an outcome showing significant effects (82–86); and only one of four meta-analyses showed a significant pooled effect (79, 87–89). Furthermore, it is difficult to interpret the findings because of the differing probiotic species, formulations and dosages used in the studies, and due to methodological problems within the studies themselves (i.e. poor compliance, recall bias). Of the various probiotic species studied, *Saccharomyces boulardii* (84, 85) and *Lactobacillus rhamnosus* GG (82, 83), both of which are stable at room temperature when lyophilized (87), appeared to be the most promising for prevention of TD with no significant side effects.

Evidence related to the preventive effects of prebiotics and synbiotics for TD is also limited (90–92). Variability in the study designs prevented comparisons as each study evaluated a different compound and used differing dosages and duration of treatment.

PREVENTION—VACCINATION AND CHEMOPROPHYLAXIS

Vaccination—Oral cholera vaccine (Dukoral®)

GRADE recommendation:

CATMAT suggests that the oral cholera vaccine (killed whole cells plus recombinant B-subunit, WC-rBS, licenced in Canada as Dukoral®)(93) not be routinely administered to Canadian travellers as a means of preventing TD; **Conditional recommendation, moderate confidence in estimate of effect versus placebo.**

Efficacy

The pooled results from three randomized controlled trials (RCTs) (94–96), as well as results from one Cochrane review (97), found no increased benefit for the oral cholera vaccine for preventing an episode of TD during travel when compared to those vaccinated with a placebo.[3] Overall, 35% of vaccinated subjects in the three studies developed TD versus 37% of non-vaccinated subjects, for a pooled RR of 0.94 and 95% confidence interval (95% CI) of 0.82 – 1.09. Additionally, these studies found no difference in effect for prevention of TD related to ETEC when compared to placebo. Lower confidence in estimate of effect can primarily be attributed to an ambiguous, potentially non-standard definition of TD in one study (94), as well as a non-standard immunization protocol in one of the other studies (95). Three observational studies (98–100) evaluating use of Dukoral® for prevention of diarrhea in returned travellers have found a beneficial effect for those who had been vaccinated when compared to travellers visiting the same clinic who had not been vaccinated. Two other observational studies found no difference in effect (101, 102). However, these five observational studies were not included in the assessment due to serious limitations with the selection of the comparison group: those who were not vaccinated had either refused vaccination or were not referred for vaccination because they were judged to be engaging in types of travel at lower risk for cholera (and thus by extrapolation also potentially at lower risk for TD). In both cases, this presents important differences in risk profile between the vaccinated and non-vaccinated groups which quite probably biased the results.

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 ETEC or cholera caused by *V. cholerae*. This indication is largely based on a field study conducted in an endemic population with a primary outcome of ETEC diarrhea (103). This study was considered in the review of the evidence but was excluded from the analysis given that it was not conducted in a traveller population that is potentially exposed to a broad spectrum of TD-causing bacteria.

Although routine use of Dukoral® for TD prevention is not recommended by CATMAT, certain selected 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 (see section below), 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 TD, young children > 2 years);
- those who are immunosuppressed due to HIV infection with depressed CD4 count or other immunodeficiency states;

[3] One study (Peltola 1991), which originally reported significantly fewer cases of TD in subjects in the vaccine group compared to the control group, did not demonstrate a significant decrease of cases in the current analysis, nor in the Cochrane review. This is due to the use of a one-sided chi-square statistical significance test in the study, compared to the two-sided test commonly used in meta-analysis.

- 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.

Harms

We were unable to assess with GRADE the safety of the inactivated oral cholera vaccines due to insufficient detail provided on adverse events. No serious adverse reactions were recorded and no differences were observed between vaccine and placebo groups in each of the three RCTs, except for a slightly higher number of "gastrointestinal symptoms" in the placebo group of one study (94).

Other vaccines

Some other vaccination interventions currently being developed include an oral ETEC-specific vaccine (killed ETEC whole cells plus recombinant cholera B-subunit), an ETEC LT subunit vaccine delivered by transcutaneous patch (LT patch), and a live attenuated oral cholera vaccine (CVD 103 HgR). A GRADE assessment of these interventions was not conducted since they are still in varying stages of clinical development and are not currently licenced in Canada. Two RCTs (96, 104) found no increased benefit for the oral ETEC vaccine for preventing either an episode of all-cause TD or ETEC-associated TD during travel when compared to those vaccinated with a placebo. The LT patch (105, 106) and the live oral cholera vaccine (107) were also evaluated in traveller populations: neither vaccine was found to increase benefit for prevention of TD as compared to placebo. A vaccine to target another pathogen responsible for TD, *Shigella*, is in early-stage human clinical trials, but cannot be evaluated at this time (108).

Viral agents such as rotavirus can also cause TD in children. A live oral rotavirus vaccine is recommended by the National Advisory Committee on Immunization (NACI) for infants starting at 6 to15 weeks of age (see NACI guidelines for details and exceptions) (109).

Antisecretory agents—Bismuth subsalicylate (BSS)

GRADE recommendation:

- CATMAT recommends that bismuth subsalicylate (BSS) be considered as an option for preventing TD for adults at significant risk, and who are willing to accept multiple doses per day (2.1–4.2g/day, divided in four doses per day); **Strong recommendation, high confidence in estimate of effect versus placebo.**
- CATMAT suggests that a lower dosage (1.05g/day) of BSS could be used to prevent TD 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.**

Efficacy

Four RCTs investigating the use of BSS versus placebo for the prevention of TD were evaluated with a GRADE assessment, of which three had an adequate definition for TD (110–112).

Overall, a strong protective effect after three to four weeks of follow-up was observed for BSS: RR = 0.55 (95% CI: 0.44 – 0.67), resulting in 250 fewer cases of TD per 1000 travellers treated. This strong effect was similarly found when restricted to those receiving a high or low dosage of BSS: RR = 0.51 (95% CI: 0.39 – 0.65) and RR = 0.65 (95% CI: 0.50 – 0.86) respectively. Similarly, there was no difference in effect found when comparing high to low dosage: RR = 0.87 (95% CI: 0.63 – 1.22). However, the results for low dosage only, as well as those for comparing high to low dosage, are of lower quality since they rely more heavily on the results of one study where there were low levels of compliance to therapy, and are limited in their ability to detect a true effect due to a lower number of subjects (imprecision). Although we were unable to assess with GRADE any differences in efficacy between liquid and tablet forms of BSS, the results do not appear to differ between the two delivery mechanisms.

Harms

We were unable to assess with GRADE the risk of developing side effects when using BSS versus placebo due to inconsistencies in reporting. The evidence does not appear to indicate any serious harm associated with BSS use. There is a probable increased risk for experiencing black tongue and black stool, although these side effects are not harmful (112). There are also reports of increases in constipation in those taking BSS (111), although this is not reported consistently across studies (110).There did not appear to be a difference in risk of side effects between high and low dosages. Bismuth subsalicylate should be avoided by those allergic to aspirin and during pregnancy. Those taking other concurrent medications should check for possible interactions with BSS. Prophylactic BSS at these doses has not been studied for periods longer than four weeks. 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 (113). Use of BSS is permitted in the case of certain children aged two years and older, based on an individual assessment of risks and benefits. BSS use is not recommended in children younger than two years old.

Antibiotics

In general, TD is a self-limited disorder, and routine use of antibiotics for prophylaxis may expose the traveller to risks which exceed those of the illness. These risks are often not well documented in studies, but theoretically would include an increased risk for carriage and infection with antibiotic resistant pathogens, antibiotic associated diarrhea and infection with *Clostridium difficile*, and other adverse reactions including hypersensitivity reactions, photosensitivity reactions, tendinopathy and cardiac arrhythmias. These types of adverse events are well documented when these antibiotics are used for other indications, although discussion of their frequency and severity is beyond the scope of this review. Therefore the risks and benefits of the use of antibiotics for diarrhea prophylaxis need to be carefully considered for each individual, and their use would not be warranted routinely. This is particularly true for children (1 to 17 years of age), since, in addition to the risks outlined above, there is a potential risk of cartilage damage and arthropathies associated with use of fluoroquinolones (see details below in discussion of harms associated with fluoroquinolones) (114, 115). Antibiotic chemoprophylaxis for TD in children should be limited to specific situations such as children with immunoglobulin A deficiency or other conditions known to significantly increase the risk and/or severity of TD. It should also be noted that TD studies in children

are non-existent and that all discussion of antibiotic use in children assumes an efficacy similar to that observed in the adult study populations. For a summary of optimal doses for each antibiotic, please see Table 2.

Antibiotics—fluoroquinolones

GRADE recommendation:

- CATMAT suggests that fluoroquinolones be considered as an option in the prevention of TD in select high-risk short-term traveller populations where chemoprophylaxis is considered essential (see below for definition of this population); **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.**

Efficacy

The results from four RCTs[4] (118–121) demonstrate that use of fluoroquinolones over a period of five to 21 days provides a significantly and substantially decreased risk of developing TD: RR = 0.12 (95% CI: 0.07 – 0.21), resulting in 293 fewer cases per 1000 travellers treated. When individual fluoroquinolones were assessed (ciprofloxacin and norfloxacin), this strong effect persisted.

Harms

We were unable to assess with GRADE the evidence on adverse reactions with fluoroquinolones due to inconsistencies in reporting. However, the studies do not indicate any significant increase in serious adverse reactions in the fluoroquinolone group as compared to the placebo group. Two studies presented the possibility of adverse skin reactions from treatment: one participant reported a case of generalized skin rash (118), while two other participants reported sunburn causing blisters (116). It is unclear if these reactions were related to treatment. While these studies may appear inconclusive, there is evidence from fluoroquinolone use in non-traveller populations suggesting that adverse reactions present a potential risk to travellers. Although no studies have been done on the risks of *Clostridium difficile* to travellers using fluoroquinolones, their use in a clinical setting has been shown to significantly increase risk for *C. difficile*-associated diarrhea (122), while there is also a rising concern about greater numbers of cases of *C. difficile* infection acquired in non-health care settings during travel (123). Additionally, safety data collected from children (6 months to 16 years old; n=2,523) participating in one of three clinical trials evaluating the efficacy of levofloxacin[5] for treating pneumonia or acute otitis media demonstrated a significantly increased risk of musculoskeletal adverse events (primarily due to reports of arthralgia) in children receiving levofloxacin as compared to non-fluoroquinolone antibiotics (115). Finally, an increased risk of tendonitis and tendon rupture, particularly the Achilles tendon, has been observed for patients taking fluoroquinolones. Although this is a rare event, risk is greater for those 60 years of age or older, those using concomitant steroid therapy,

[4] Five RCTs provided results for this comparison, but one (116) was excluded due to use of an inadequate definition of TD in the study inclusion criteria. One meta-analysis on the subject was also consulted (117).

[5] Therapy was given for 7–14 days in one study and for 10 days in the other two studies. Follow-up was for one year. Two of the studies were randomized, one was (single) blinded.

as well as in kidney, heart and lung transplant recipients (114). Due to the risk observed in non-traveller populations for adverse effects, which generally increases with duration of treatment, fluoroquinolones should only be considered as a prevention option in selected high-risk short-term travellers:

- 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 TD);
- 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).

Antimicrobial resistance

It is important to note that in the 20 to 25 years since studies were published evaluating the efficacy of fluoroquinolones to prevent TD, *in vitro* studies of returning travellers have found increased resistance of various TD-related pathogens to fluoroquinolones. Resistance levels range from one to 10% for *E. coli* pathogens (ETEC and EAEC) (124–127) and are much higher (71% to 84%) for *Campylobacter* strains tested from military personnel stationed in Thailand and travellers visiting Nepal (128, 129). One other study found no resistance to *Salmonella* for ciprofloxacin and norfloxacin (130). Several studies also found elevated resistance to nalidixic acid treatment for several key pathogens (124, 127, 129, 131), with rates being particularly high in travellers to the Indian subcontinent (64% in one study, (131)). This is of particular concern since it has been demonstrated that nalidixic acid-resistant strains of pathogens are associated with treatment failure when using fluoroquinolones to treat TD (130). The above-mentioned studies evaluated resistance *in vitro* and results may not necessarily correlate with actual clinical response to treatment. The antimicrobial resistance evidence therefore cannot be assessed using GRADE. However, the extent to which this *in vitro* fluoroquinolone antimicrobial resistance has been documented, specifically for the geographic regions of the Indian subcontinent (India and Nepal in particular) and Southeast Asia (Thailand in particular), leads CATMAT to suggest that alternative preventive measures be explored for high-risk travellers visiting these regions.

Antibiotics—azithromycin

We did not find any evidence to evaluate the use of azithromycin in the prevention of TD. Studies in several low and middle income countries evaluating the efficacy of campaigns to prevent trachoma through mass treatment with azithromycin noted a reduced risk for acute diarrhea in children 14 years of age and under when evaluated up to one month after treatment (132–134). Azithromycin may be an acceptable choice for prevention in pediatric patients or in patients for whom fluoroquinolones are contra-indicated, when antibiotic prophylaxis is justifiable.

Antibiotics—rifaximin

GRADE recommendation:

- CATMAT suggests that rifaximin be considered as an option in the prevention of TD; **Conditional recommendation, moderate confidence in estimate of effect versus placebo. Balance of benefits and harms based on available evidence on antimicrobial resistance patterns.**

Efficacy

An assessment of five RCTs (135–139) found a strong protective effect against TD when rifaximin was administered for two to three weeks during travel as compared to placebo:[6] RR = 0.42 (95% CI: 0.33 – 0.53), resulting in 213 fewer cases per 1000 travellers treated. The quality of the evidence was downgraded for potential publication bias due to the fact that results were unavailable for one large study (n=660) registered on the U.S. government's clinical trials database and completed in 2008 (141).

Antimicrobial resistance

Evidence of antimicrobial resistance patterns associated with rifaximin use in travellers was difficult to assess. Contrary to fluoroquinolones, there are no established thresholds for resistance based on minimum inhibitory concentration (MIC). Evidence on *in vitro* activity in samples taken from travellers is mixed although generally favourable. One study (126) demonstrated that rifaximin showed intermediate activity against all pathogens evaluated versus high activity for the quinolones, whereas a more recent study (127) found rifaximin exhibited good activity against all pathogens. Another study (131) showed that rifaximin MIC levels for strains of ETEC and EAEC did not change between 1997 and 2008 whereas they did increase substantially for quinolones and azithromycin. However, *in vitro* testing on mechanisms of rifaximin resistance has revealed that high level resistance can be conferred on strains of ETEC and EAEC with a single step mutation. It appears that selection of resistance to rifaximin is easier than for other commonly used antibiotics (142). More definitive study of antimicrobial resistance to rifaximin will need to be conducted before a more conclusive assessment of its long-term efficacy can be given.

Harms

We were unable to assess with GRADE the safety of rifaximin for prevention of TD due to inconsistencies in reporting on adverse events. However, all studies stated that there were no serious adverse events and no difference in number of adverse events between rifaximin and placebo groups. There are no data on the use of this agent in children (≤12 years old) and CATMAT therefore does not recommend the use of rifaximin in this age group.

TREATMENT

Antisecretory agents—Bismuth subsalicylate (BSS)

We were unable to make a GRADE assessment of BSS use for treatment. Of the four RCTs evaluating the efficacy of BSS compared to placebo in a traveller population, two had an inadequate definition of TD (143). Of the remaining two studies (144, 145) there was a lack

[6] Two published meta-analyses arrived at a similar conclusion (117, 140).

of commonality in the outcomes assessed. The available evidence appears to indicate a beneficial effect: the two studies using a valid definition of TD found an increased association with absence of diarrhea after 24 hours (144) and cure from all TD symptoms after 48 hours (145), as well as significant albeit modest reductions in duration of diarrhea and mean number of stools passed. We were unable to formally assess the safety of BSS. Two of the three studies made mention of adverse events, one of which indicated that black tongue and black stool were seen in high numbers (145). However, there were no serious adverse reactions reported in any of these studies and no other significant difference in occurrence of events between treatment groups. Treatment with BSS is not recommended in children younger than 2 years old and is contraindicated in acetylsalicylic acid allergy (113).

Antimotility agents—Loperamide

GRADE recommendation:

- CATMAT suggests that the antimotility agent loperamide be considered as an option in the treatment of TD; **Conditional recommendation, low to moderate confidence in estimate of effect compared to placebo.**

Efficacy

Three RCTs were identified which had an adequate definition of TD and evaluated the efficacy of loperamide compared to placebo in traveller populations generally using a three-day treatment regimen (146–148). However, due to inconsistency across these studies in outcomes being assessed, we decided to increase the evidence base by including studies with non-traveller populations in our assessment (149–151), although this requires us to downgrade the quality of the evidence for indirectness. Confidence in the estimate of effect was also lowered for three of the four outcomes assessed with GRADE due to an insufficient number of study subjects. Two studies (150, 151) in the non-traveller population found that loperamide was associated with a significant increase in first relief from acute diarrhea after 4, 12 and 24 hours of treatment when compared to placebo: RR for first relief from acute diarrhea after 4 hours = 1.69 (95% CI: 1.17 – 2.45), resulting in 145 more cases of first relief after 4 hours per 1000 travellers treated. Similarly, two studies (of which one was in the traveller population) also observed this beneficial effect for complete relief of acute diarrhea after 24 hours (150) and 48 hours (148). The evidence on reduction of duration of diarrhea, however, is mixed with two studies (147, 150) showing a significantly reduced time to complete relief from diarrhea of approximately 18 to 24 hours as compared to placebo, while two other studies (148, 149) found non-significant reductions in duration for loperamide. Finally, there was evidence to support a small but significant reduction in the intensity of diarrhea: an average of 1.6 fewer stools during the first 24 hours of treatment (146, 149) and an average of 2.3 fewer unformed stools after 48 hours of treatment (148).

We were unable to assess with GRADE the efficacy of loperamide as compared to BSS due to a limited number of studies, combined with a lack of commonality in outcomes assessed. However, two studies (152, 153) with an adequate definition of TD did compare these two therapies directly in the traveller population and the results appear to indicate an advantage for loperamide. One of the studies (153) evaluated duration of diarrhea and found that

loperamide significantly reduced the mean time to last unformed stool by approximately 10 hours when compared to BSS. The same study also found that loperamide treatment was significantly associated with no further dose needed after 24 hours. Finally, both studies evaluated intensity of diarrhea and found persons receiving loperamide experienced a small but significant reduction in average number of stools during various time periods within the first 24 hours of treatment when compared to those receiving BSS.

Loperamide use in travelling children has not been studied. However, one RCT conducted in children aged two to 11 with acute diarrhea (154) 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. Dosages differ by age group (see Table 2) and treatment should not exceed two days. Loperamide should not be administered to children under two years of age (113).

Harms

We were unable to formally assess the safety of loperamide use due to insufficient detail provided on adverse events. However, all of the relevant studies mention that there were no significant differences in adverse events between study populations and that no serious adverse events were recorded.

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 (155). Lomotil has a less favourable side effect profile, and it has not been studied in the treatment of TD.

Loperamide in combination with antibiotics

GRADE recommendation:

- CATMAT suggests that the use of the antimotility agent loperamide in conjunction with antibiotic therapy be considered as an option in the treatment of TD; **Conditional recommendation, moderate to high confidence in estimate of effect compared to antibiotic use alone.**

Efficacy

Six RCTs[7] assessed various outcomes related to this intervention, of which five used an adequate definition of TD (147, 156–159). One meta-analysis evaluating this intervention was also consulted (160). Results from four studies (147, 156, 158, 159) evaluating cure rates found that loperamide used in combination with an antibiotic was significantly associated with a greater cure after 24 hours and 48 hours of therapy when compared to antibiotic use alone: RR for complete relief from TD after 24 hours=1.55 (95% CI: 1.28 – 1.86), resulting in 200 more cases of complete relief after 24 hours per 1000 travellers treated. These same four studies also evaluated treatment failures and found that adding loperamide to antibiotic therapy significantly reduced the risk of a failure. Estimates of effect for two of the four outcomes were rated down due to substantial variation between studies in the observed direction of effect (inconsistency). Given the relatively mild nature of most episodes of TD,

[7] Although studies evaluating trimethoprim/sulfamethoxazole were generally excluded from our analyses due to widespread antibiotic resistance, these studies were retained for this intervention since the focus for evaluation is the addition of loperamide to antibiotic use and not the antibiotic itself.

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 antimotility or antibiotic alone is unsuccessful.

Harms

We were unable to formally assess safety of adjunctive loperamide use due to insufficient detail provided on adverse events. However, all of the relevant studies mention that there were no significant differences in adverse events between study populations and that no serious adverse events were recorded.

Antibiotics—fluoroquinolones

GRADE recommendation:

- CATMAT suggests that fluoroquinolones be considered as an option in the treatment of TD; **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.**

Efficacy

Nine RCTs assessed fluoroquinolone for treatment of TD versus placebo, of which six used an adequate definition of TD (161–166). One Cochrane review evaluating this intervention was also consulted (167). Three of these studies evaluated cure rate (162, 163, 165), of which two (162, 165) found an overall increased cure after 72 hours for norfloxacin when compared to placebo: RR = 1.81 (95% CI: 1.39 – 2.37), resulting in 322 more cases of cure after 72 hours per 1000 travellers treated. The other study found ofloxacin use increased cure after 48 hours and after five days using either three-day or five-day treatment regimens, while the three-day regimen also increased cure after 24 hours when compared to placebo (163). The estimate of effect was rated down due to imprecision. Although we were unable to formally assess reductions in diarrhea duration, four studies (161, 163, 165, 166) found significant reductions in time to last unformed stool in the treatment group, ranging from 28 to 52 hours faster than those taking placebo.

Harms

The evidence from the studies evaluated does not appear to indicate any serious harm associated with fluoroquinolone use. Three of the nine studies provided sufficient results to assess the safety of fluoroquinolone use (163, 166, 168) and the results indicate that there is a possible increased risk of adverse event for those taking fluoroquinolones compared to placebo: RR = 1.39 (95% CI: 1.05 – 1.83), resulting in 80 more travellers with some sort of adverse event per 1000 travellers treated. Some of the more common adverse events reported include headaches, constipation, nausea and fatigue, although there is no clear evidence of greater risk of developing any individual symptom for fluoroquinolone users. Indeed, the quality of this evidence is very low, most notably due to the lack of standardized reporting of adverse events across studies and inconsistency in estimates of effect among the three studies. Please also refer to the Prevention section of this statement for theoretical risks of fluoroquinolone use and *C. difficile* infection, as well as risks for cartilage damage and arthropathies.

Antimicrobial resistance

Fluoroquinolones should be used with caution in situations where elevated levels of resistance have been documented (see section on chemoprophylaxis).

Antibiotics—azithromycin

GRADE recommendation:

- CATMAT suggests that azithromycin be considered as an option in the treatment of TD; **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.**

Efficacy

No studies were found which evaluated the efficacy of azithromycin as compared to placebo in traveller populations. There were five RCTs which directly compared the efficacy of azithromycin to fluoroquinolones[8] in the treatment of TD, of which four had an adequate definition of TD (169–172). For three of the outcomes of interest, no difference in efficacy was found between the two treatment groups: recovery from TD after 24 hours (RR = 0.79, 95% CI: 0.61 – 1.01); recovery after 72 hours (RR = 1.16, 95% CI: 1.00 – 1.33); and treatment failure (RR = 1.02, 95% CI: 0.45 – 2.32). However, for rapid or immediate cure from TD, azithromycin was associated with a reduced effect compared to fluoroquinolones: RR = 0.46 (95% CI: 0.25 – 0.84). Conversely, for cure from TD after 48 hours of treatment, azithromycin was associated with a greater effect compared to fluoroquinolones: RR = 1.34 (95% CI: 1.08 – 1.66). Although we were unable to assess duration of diarrhea using GRADE, three of the four studies providing some information on time to last unformed stool (170–172) demonstrated no difference in duration between azithromycin and fluoroquinolones. Taken together, these results suggest that azithromycin's ability to provide relief from TD is equivalent to that of fluoroquinolones. However, confidence in the estimate of effect is low 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).

Antimicrobial resistance

A search of the literature on antimicrobial resistance patterns in azithromycin use for TD was inconclusive. One study demonstrated that azithromycin exhibited high activity against all TD-related pathogens (126), while another demonstrated that the concentrations of this antibiotic needed to inhibit travel-related ETEC and EAEC have been increasing since the late 1990s (173). Although azithromycin is recommended as an alternative to fluoroquinolones in Southeast Asia due to resistance patterns observed in that region, two studies have demonstrated relatively elevated levels of resistance in *Campylobacter* in both travellers to Nepal (129) and U.S. military stationed in Thailand (128). On the other hand, results from *in vitro* studies have not been proven to predict a failed clinical outcome.

[8] Levofloxacin and ciprofloxacin were the two fluoroquinolones evaluated in these studies.

Harms

The evidence does not appear to indicate any serious harm associated with use of azithromycin. Two studies assessed specific adverse events (nausea and vomiting) in these two treatment populations (171, 172) and found a greater risk of nausea immediately following first treatment with azithromycin: RR = 6.23 (95% CI: 1.48 – 26.26), resulting in 68 more travellers with nausea in the first 30 minutes of treatment per 1000 treated with azithromycin as compared to those treated with fluoroquinolones. Otherwise, there were no differences in other measures of nausea and vomiting. The quality of this evidence was low, primarily due to imprecision related to small study population and number of events, as well as the fact that one of the four studies was less comparable since it included loperamide as an adjunct to therapy.

Antibiotics—rifaximin

GRADE recommendation:

- CATMAT suggests that rifaximin be considered as an option in the treatment of TD; **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.**

Efficacy

Two relatively recent RCTs (166, 174) evaluated the efficacy of rifaximin as compared to placebo in traveller populations. Rifaximin was associated with a higher percentage of travellers cured of TD (RR = 1.29, 95% CI: 1.15 – 1.45, resulting in 177 more travellers cured of TD at the end of follow-up per 1000 treated) and reduced the risk of treatment failure (RR = 0.50, 95% CI: 0.38 – 0.67) compared to placebo. Two RCTs also directly compared the efficacy of rifaximin to that of the fluoroquinolone ciprofloxacin (166, 175). There was no significant difference between rifaximin and fluoroquinolones with respect to proportion cured of TD (RR = 0.98, 95% CI: 0.90 – 1.07), or treatment failure (RR = 1.81, 95% CI: 0.96 – 3.43). The estimate of effect for treatment failure was rated down due to imprecision. These results suggest that treatment of TD with rifaximin has the same efficacy as treatment with fluoroquinolones.

Antimicrobial resistance

Antimicrobial resistance issues were still difficult to assess at the time of this writing and will need to be closely monitored. Please see the section on chemoprophylaxis with rifaximin for discussion of this subject.

Harms

Rifaximin appeared to be safe, with no difference reported in the proportion of adverse events between treatment and placebo groups (RR = 0.96, 95% CI: 0.83 – 1.11), nor between the rifaximin and fluoroquinolone treatment groups (RR = 1.01, 95% CI: 0.76 – 1.35). There are no data on the use of this agent in children (≤12 years old) and CATMAT therefore does not recommend the use of rifaximin in this age group.

Antibiotic treatment: conclusions and other considerations

As a general rule, antibiotic use for treatment should be limited as much as possible due to the adverse events and antimicrobial resistance patterns discussed above. If symptoms from TD are mild, the preferred mode of treatment should be oral rehydration and loperamide (or BSS). However, should this line of treatment fail or more serious symptoms be present in the traveller, antibiotic use may be justified. For more severe cases of TD and whenever feasible, it is also advisable to obtain culture and antibiotic sensitivity for known pathogens in order to facilitate optimal choice of treatment regimen.

One limitation of assessing efficacy and harm of antibiotic use for treatment of TD in children is the lack of studies evaluating this age group. As such, all discussion of antibiotic use in children assumes an efficacy similar to that observed in the adult study populations. Some specific clinical observations on children, however, may be made. 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. Otherwise, azithromycin should be used in this age group or cefixime if azithromycin is contraindicated (113). There is evidence that cefixime is efficacious against several of the pathogens which cause TD. However, an increase in cases of antibiotic-associated colitis has been noted in at least one pediatric population after treatment for profuse diarrhea with cefixime (176). Finally, while reports exist of an increased risk for developing hemolytic-uremic syndrome (HUS) in children given antibiotics for treatment of enterohemorrhagic *Escherichia coli* (EHEC) (177), this should not be a major consideration in the decision to treat TD empirically with antibiotics. EHEC is a pathogen primarily found in children in higher income countries and is rarely seen in TD studies (10). Similarly, there is an absence of HUS cases in the TD literature, suggesting that this is a very rare complication amongst travellers.

MANAGING TD SYMPTOMS—REHYDRATION

Oral replacement of fluid levels and electrolytes is of primary importance in managing any case of TD, and most existing recommendations are based on treatment of acute diarrhea. Children, particularly those two years old and younger, are at high risk for dehydration. Many oral rehydration solutions (ORS) formulas are available at pharmacies both in Canada and overseas, while solutions can also be concocted at home (see Table 3 for more information on preparing ORS). The traditional ORS, however, does not reduce diarrhea duration or severity. Since 2002, the WHO has been recommending the use of a reduced osmolarity ORS which does reduce diarrhea symptoms (178). Reduced osmolarity ORS can be approximated by diluting two parts standard ORS with one part boiled or treated water (179). Commercial or WHO-type ORS products are commonly used at a dose of 50 mL/kg for mild dehydration (3–5% body weight loss). However, parents often have difficulty properly assessing a child's hydration status, and should be strongly advised to seek medical attention when any significant dehydration is suspected[9] (179). Evidence from clinical studies evaluating a variety of dietary options demonstrate that an unrestricted diet initiated early on in the rehydration process has

[9] For more information on dehydration and diarrhea in children, parents are encouraged to refer to the following Canadian Pediatric Society website: www.caringforkids.cps.ca/handouts/dehydration_and_diarrhea

no negative effects on the course or symptoms of diarrhea when compared to ORT alone (180). Since early feeding does not appear to be detrimental and is beneficial in terms of improved nutrition, a regular age-appropriate diet should be re-established at an early stage in rehydration. This includes any type of milk (full-strength, human, animal, containing lactose, etc.) and most foods. However, although evidence is lacking, it is suggested that foods high in fat and simple sugars should be avoided due to a tendency of fats to delay gastric emptying and the ability of simple sugars to exacerbate diarrhea through osmotic effects (180). Fluids should be consumed at a rate to allay thirst and maintain pale-coloured urine.

TREATMENT OF TD UPON RETURN FROM TRAVEL

Any febrile traveller with diarrhea who has visited a malaria endemic area must have blood films performed immediately to rule out malaria. Patients with severe TD not responding to empiric therapy and those with severe underlying medical conditions, immunosuppression, or grossly bloody stools should be referred to a specialist for further evaluation. Travellers with persistent diarrhea lasting more than 14 days, despite therapy, should be managed according to the CATMAT statement of persistent diarrhea in the returned traveller (3).

VALUES AND PREFERENCES

Recommendations made using GRADE need to take into account the values and preferences of the patient for each of the treatment and prevention options. Unfortunately, there is limited information available for these preferences among the travelling population. One study did assess travellers' willingness to take antibiotic chemoprophylaxis as well as various treatment regimens for TD (181). A relatively high percentage of travellers indicated they preferred not taking antibiotics for prevention of TD. There was also high variability between North American and European respondents with respect to their preferences for antidiarrheal treatment as well as their ability to correctly assess their level of TD risk for their chosen country of travel. These factors serve to reinforce the conditional nature of CATMAT recommendations for these preventive and treatment interventions.

CONCLUSIONS AND RESEARCH NEEDS

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 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. For this latter point, 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, we have no reliable evidence on the presence or magnitude of the risk in the case of TD. As such, 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

serve to 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 in order to make a more definitive recommendation for or against its use in specific populations. Of equal importance will be the systematic review of studies evaluating the efficacy of other vaccines currently in development which target TD-related pathogens, most notably ETEC vaccines. Finally, CATMAT also recommends further research on specific species of probiotics, compounds of prebiotics or combinations of the two (i.e., synbiotics) in order to better evaluate their efficacy in preventing TD.

ACKNOWLEDGEMENTS

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CATMAT gracefully acknowledges the contribution of Francesca Reyes-Domingo for her assistance in developing this statement.

TABLES

TABLE 1: List of studies* considered for inclusion in analysis of efficacy of TD prevention and treatment

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Oral cholera vaccine (Dukoral®) for prevention of TD					
Peltola 1991	Finnish travellers to Morocco, age ≥15yrs n=615	WC-BS vaccine, 2 doses given 3 to 21 days before departure vs. placebo	Not indicated	Occurrence of TD: 0.77 (0.59, 1.00)	**Included in analysis** Definition of TD: unclear if quantity of loose stools assessed.
Scerpella 1995	U.S. college students in Mexico, age ≥18yrs n=502	WC-rBS vaccine, 2 doses given upon arrival and 10 days later vs. placebo	35 days from first dose	Occurrence of TD: 1.04 (0.87, 1.24)	**Included in analysis** Vaccine administered post-arrival.
Wiedermann 2000	Travellers to tropical and subtropical destinations, adults and children n=125	WC-rBS, 2 doses given 7 to 30 days before departure vs. placebo	Upon return (range 7–23 days)	Occurrence of TD: 1.28 (0.68, 2.39)	**Included in analysis** Definition of TD: did not include an enteric symptom.
Clemens 1988	Endemic population of women and children in rural Bangladesh n=49,612	WC-BS vaccine, 3 doses given 6 weeks apart vs. WC vaccine only and placebo	14–365 days	Occurrence of TD: 0.33 (0.13, 0.84)	**Excluded from analysis** Study conducted in non-traveller population.
Lopez-Gigosos 2007 (observational study)	Spanish travellers to high-risk cholera regions, adults (mean age=35yrs) n=237	WC-rBS, doses and schedule not given vs. travellers at same clinic prior to vaccine availability or refused vaccine	Upon return (range 7–134 days)	Occurrence of TD: 0.57 (0.38, 0.85)	**Excluded from analysis** Retrospective cohort study. Risk profile of comparison group differs from that of vaccinated group.

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Lopez-Gigosos 2009 (observational study)	Spanish travellers to high-risk cholera regions, adults n=362	WC-rBS, doses and schedule not given vs. travellers at same clinic prior to vaccine availability or refused vaccine	Upon return (range 14–154 days)	Occurrence of TD: 0.57 (0.41, 0.81)	**Excluded from analysis** Retrospective cohort study. Risk profile of comparison group differs from that of vaccinated group.
Torrell 2009 (observational study)	Spanish adventure travellers at high risk for TD, age 18–35yrs n=658	WC-rBS, 2 doses given minimum 7 to 14 days before departure vs. travellers at same clinic prior to vaccine availability or refused vaccine	30–90 days after return	Occurrence of TD: 0.44 (0.33, 0.58)	**Excluded from analysis** Retrospective cohort study. Risk profile of comparison group differs from that of vaccinated group.
Gabutti 2012 (observational study)	Italian travellers to areas at risk for cholera and TD, adults (mean age=38yrs) n=296	WC-rBS, 2 doses given minimum 7 to 14 days before departure vs. unvaccinated (no further details)	Upon return (no further details)	Occurrence of TD: 0.68 (0.41, 1.15)	**Excluded from analysis** Retrospective cohort study. Risk profile of comparison group differs from that of vaccinated group.
Lopez-Gigosos 2013 (observational study)	Spanish travellers to high-risk cholera regions, adults (mean age=35yrs) n=1074	WC-rBS, 2 doses given minimum 7 to 14 days before departure vs. travellers at same clinic judged as low-risk for cholera and travelling to same regions as vaccinated group	7–14 days after return	Occurrence of TD: 0.91 (0.78, 1.07)	**Excluded from analysis** Prospective cohort study. Risk profile of comparison group differs from that of vaccinated group.
Bismuth subsalicylate (BSS) for the prevention of TD					
DuPont 1980	U.S. college students in Mexico, age not given n=128	4.2g BSS/day (liquid), four doses of 1.05g vs. placebo	21 days	Occurrence of TD: 0.37 (0.23, 0.61)	**Included in analysis**

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Steffen 1986	Swiss travellers to tropical countries, age 16–70yrs a) n=231 b) n=160 c) n=143 d) n=156	2.1g or 1.05g BSS/day (tablet) vs. placebo 2.1g BSS/day (tablet), two doses of 1.05g vs. placebo 1.05g BSS/day (tablet), two doses of 525mg vs. placebo 2.1g BSS/day vs. 1.05g BSS/day	30 days	a) Occurrence of TD: 0.68 (0.53, 0.87) b) Occurrence of TD: 0.68 (0.50, 0.91) c) Occurrence of TD: 0.68 (0.50, 0.94) d) Occurrence of TD: 0.99 (0.61, 1.41)	**Included in analysis** 21% loss to follow up. 27% poor compliance to treatment.
DuPont 1987	U.S. college students in Mexico, age ≥19yrs a) n=172 b) n=109 c) n=121 d) n=114	2.1g or 1.05g BSS/day (tablet) vs. placebo 2.1g BSS/day (tablet), four doses of 524mg vs. placebo 1.05g BSS/day (tablet), four doses of 262mg vs. placebo 2.1g BSS/day vs. 1.05g BSS/day	21 days	a) Occurrence of TD: 0.49 (0.30, 0.80) b) Occurrence of TD: 0.35 (0.16, 0.74) c) Occurrence of TD: 0.60 (0.35, 1.03) d) Occurrence of TD: 0.58 (0.25, 1.31)	**Included in analysis**
Graham 1983	In-patient, healthy young adults, age not given n=31	2.1g BSS/day (tablet), four doses of 600mg vs. placebo	4 days	Occurrence of TD: 0.24 (0.06, 0.92)	**Excluded from analysis** Number of unformed stools less than classic TD definition.
Fluoroquinolones for the prevention of TD					
Johnson 1986	U.S. college students in Mexico, age not given n=120	Norfloxacin 400mg once daily for 14 days vs. placebo	21 days	Occurrence of TD: 0.12 (0.04, 0.31)	**Included in analysis**

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Wiström 1987	Swedes travelling outside of Northern Europe, mean age=45yrs n=127	Norfloxacin 200mg twice daily for 5–21 days vs. placebo	Up to 23 days	Occurrence of TD: 0.16 (0.04, 0.69)	**Included in analysis** Association persists when stratified by area of travel (high vs. low risk).
Scott 1990	U.S. military personnel in Egypt, mean age=26yrs n=262	Norfloxacin 400mg once daily for 7 days vs. placebo	11 days	Occurrence of TD: 0.07 (0.02, 0.30)	**Included in analysis**
Heck 1994	U.S. volunteers in Honduras, age 18–70yrs n=230	Ciprofloxacin 500mg once daily for 15 days vs. placebo	20 days	Occurrence of TD: 0.15 (0.06, 0.38)	**Included in analysis**
Rademaker 1989	Dutch travellers to Tunisia, mean age=28yrs n=54	Ciprofloxacin 500mg once daily for 7 days vs. placebo	10 days	Occurrence of TD: 0.06 (0.01, 0.42)	**Excluded from analysis** Number of unformed stools less than classic TD definition.
Rifaximin for prevention of TD					
DuPont 2005	U.S. college students in Mexico, age not given n=219	Rifaximin 200mg once daily for 14 days vs. placebo Rifaximin 200mg twice daily for 14 days vs. placebo Rifaximin 200mg three times daily for 14 days vs. placebo	14 days	Occurrence of TD (all treatment arms combined): 0.27 (0.17, 0.43) Occurrence of TD (600mg arm only): 0.24 (0.12, 0.50)	**Included in analysis**
Armstrong 2010	U.S. military personnel in Turkey, median age=36yrs n=100	Rifaximin 1100mg once daily for 14 days vs. placebo	14 days	Occurrence of TD: 0.33 (0.09, 1.13)	**Included in analysis** Possible lack of concealment of treatment allocation.

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Martinez-Sandoval 2010	U.S. college students in Mexico, age not given n=210	Rifaximin 600mg once daily for 14 days vs. placebo	14 days	Occurrence of TD: 0.32 (0.19, 0.54)	**Included in analysis**
Flores 2011	U.S. college students in Mexico, mean age=25yrs n=101	Rifaximin 550mg once daily for 14 days vs. placebo	14 days	Occurrence of TD: 0.72 (0.27, 1.92)	**Included in analysis**
Zanger 2013	German travellers to south and southeast Asia, 18–64yrs n=258	Rifaximin 200mg twice daily for 6–28 days (duration of travel) vs. placebo	6–28 days	Occurrence of TD: 0.63 (0.42, 0.96)	**Included in analysis**
Bismuth subsalicylate (BSS) for treatment of TD					
DuPont 1977	U.S. college students in Mexico, age not given n=137	4.2g BSS (liquid), 525mg every half-hour for 3.5 hours or 8.4g BSS (liquid), 1.05g every half-hour for 3.5 hours vs. placebo	24 hours	Presence of diarrhea after 24hrs (treatment arms combined): 0.39 (0.21, 0.76)	**Included in review, excluded from analysis** Some Latin American students included in study group.
Steffen 1988a	U.S. college students in Mexico, age not given n=112	4.2g BSS/day (liquid), 525mg every half-hour max. 8 doses, for two days vs. placebo	72 hours	Complete cure after 48hrs: 1.33 (0.86, 2.04)	**Included in review, excluded from analysis** Some Latin American students included in study group.
Steffen 1988b	European travellers to West Africa, age not given n=133	4.2g BSS/day (liquid), 1.05g every hour max. 4 doses, for two days vs. placebo	48 hours	Complete cure after 48hrs: 1.82 (1.11, 2.99)	**Excluded from analysis** Number of unformed stools less than classic TD definition.

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Steffen 1988c	European travellers to developing countries, mean age=36yrs n=830	4.2g BSS (liquid), 525mg every half-hour for 3.5 hours, for two days vs. placebo	48 hours	Complete cure after 48hrs: 1.38 (1.09, 1.75)	**Excluded from analysis** Number of unformed stools less than classic TD definition. Large loss to follow-up. Poor compliance to treatment.
Loperamide for treatment of TD					
Hughes 1995	British patients in general practice, aged 18–75yrs n=202	2mg loperamide plus 2mg after each loose stool, max. 16mg, for three days vs. placebo	72 hours	First relief of diarrhea after 4hrs: 1.55 (0.98, 2.45) First relief of diarrhea after 12hrs: 1.51 (1.05, 2.18) First relief of diarrhea after 24hrs: 1.38 (1.06, 1.79) Complete relief of diarrhea after 24hrs: 1.48 (1.05, 2.10)	**Included in analysis** Not a traveller population.
Steffen 1988c	European travellers to developing countries, mean age=36yrs n=800	4mg loperamide plus 2mg after each loose stool, max. 8mg, for two days vs. placebo	48 hours	Complete relief of diarrhea after 24hrs: 1.74 (1.31, 2.31)	**Excluded from analysis** Number of unformed stools less than classic TD definition. Large loss to follow-up. Poor compliance to treatment.
Van Loon 1989	Expatriates living in Bangladesh, mean age=36yrs n=50	4mg loperamide plus 2mg after each loose stool, max. 16mg, for two days vs. placebo	5 days	Mean number of stools after 24hrs (mean difference): -1.40 (-3.38, 0.58)	**Included in analysis**
Bergström 1986	Swedish outpatients, median age=32yrs n=112	4mg loperamide plus 2mg after each loose stool, max. 16mg, for two days vs. placebo	5 days	Mean number of stools after 24hrs (mean difference): -1.75 (-3.55, 0.05)	**Included in analysis** Not a traveller population.

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
DuPont 1990	U.S. college students in Mexico, mean age=26yrs n=203	4mg loperamide plus 2mg after each loose stool, max. 8mg, for two days vs. 4.9g BSS/ day, 612.5mg every 30–60min max. 8 doses, for two days	48 hours	No additional doses needed after 24hrs: 1.75 (1.35, 2.28)	**Included in review, excluded from analysis** No blinding (open label study).
Johnson 1986	U.S. students in Latin America, age not given n=156	4mg loperamide plus 2mg after each loose stool, max. 16mg, for two days vs. 30mL BSS each half-hour for 3.5 hours, for two days	48 hours	Median number of stools after 4 hours (median difference): -0.5 (cannot calculate 95%CI: p<0.004)	**Included in review, excluded from analysis** No mean and standard deviation provided.
Steffen 1988c	European travellers to developing countries, mean age=36yrs n=800	4mg loperamide plus 2mg after each loose stool, max. 8mg, for two days vs. placebo	48 hours	Complete relief of diarrhea after 24hrs: 1.74 (1.31, 2.31)	**Excluded from analysis** Number of unformed stools less than classic TD definition. Large loss to follow-up. Poor compliance to treatment.
Loperamide combined with antibiotics for the treatment of TD					
Ericsson 1990	U.S. college students in Mexico, mean age=24yrs n=92	TMP/SMX 160mg/800mg, twice daily and loperamide 4mg plus 2mg after each loose stool max. 16mg vs. loperamide only (same dosage) plus placebo, 3 days	5 days	Clinical cure at 24hrs: 1.97 (1.34, 2.90) Clinical cure at 48hrs: 1.24 (0.98, 1.55) Clinical cure at 72hrs: 1.18 (1.03, 1.35) Treatment failure: 0.33 (0.04, 3.04)	**Included in analysis**

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Petruccelli 1992	U.S. military personnel in Thailand, age not given n=97	Ciprofloxacin 750mg, single dose and loperamide 4mg plus 2mg after each loose stool max. 16mg vs. loperamide only (same dosage) plus placebo, 3 days	72 hours	Clinical cure at 24hrs: 1.06 (0.84, 1.34) Clinical cure at 48hrs: 1.10 (0.83, 1.45) Clinical cure at 72hrs: 0.86 (0.75, 1.00)	**Included in analysis**
Ericsson 1997	U.S. college students in Mexico, mean age=27yrs n=110	Ofloxacin 400mg, single dose and loperamide 4mg plus 2mg after each loose stool max. 16mg vs. loperamide only (same dosage) plus placebo, 3 days	5 days	Treatment failure: 0.12 (0.01, 2.09)	**Included in analysis** Single blind study.
DuPont 2007	U.S. college students in Mexico, mean age=26yrs n=206	Rifaximin 200mg three times daily and loperamide 4mg plus 2mg after each loose stool max. 16mg vs. loperamide only (same dosage) plus placebo, 2 days	5 days	Clinical cure at 24hrs: 1.79 (1.17, 2.75) Clinical cure at 48hrs: 1.30 (0.99, 1.70) Clinical cure at 72hrs: 1.10 (0.91, 1.34)	**Included in analysis**
Ericsson 2007	U.S. college students in Mexico, mean age=23yrs n=112	Azithromycin 500mg, single dose and loperamide 4mg plus 2mg after each loose stool max. 16mg vs. loperamide only (same dosage) plus placebo, 2 days	4 days	Clinical cure at 24hrs: 1.42 (1.11, 1.82) Clinical cure at 48hrs: 1.27 (1.07, 1.51) Clinical cure at 72hrs: 1.23 (1.06, 1.42) Treatment failure: 0.17 (0.04, 0.71)	**Included in analysis**

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Taylor 1991	U.S. military personnel in Egypt, age not given n=97	Ciprofloxacin 500mg, twice daily and loperamide 4mg plus 2mg after each loose stool max. 16mg vs. loperamide only (same dosage) plus placebo, 3 days	72 hours	Clinical cure at 24hrs: 1.23 (0.98, 1.55) Clinical cure at 48hrs: (0.81, 1.16)	**Excluded from analysis** Number of unformed stools less than classic TD definition.
Fluoroquinolones for the treatment of TD					
Wiström 1989	Swedish travellers to developing countries, mean age=38yrs n=106	Norfloxacin 400mg twice daily for three days vs. placebo	72 hours	Cured of TD at 72hrs: 1.97 (1.32, 2.95)	**Included in analysis**
Mattila 1993	Finnish travellers to Morocco, mean age=42yrs n=106	Norfloxacin 400mg twice daily for three days vs. placebo	72 hours	Cured of TD at 72hrs: 1.69 (1.18, 2.42)	**Included in analysis**
DuPont 1992	U.S. college students in Mexico, mean age=28yrs n=232	Ofloxacin 300mg twice daily for three days or five days vs. placebo	5 days	Adverse events 7.84 (0.45, 135.58) Duration of diarrhea N/A	**Adverse events: included in analysis** **Other outcomes: included in review, excluded from analysis**
Steffen 1993	Guests in a hotel in The Gambia, mean age=37yrs n=195	Fleroxacin 400mg, single dose or for two days vs. placebo	72 hours	Adverse events: 1.71 (1.25, 2.34) Cured of TD at 72hrs: 1.71 (1.25, 2.34)	**Adverse events: included in analysis** **Other outcomes: Excluded from analysis** Number of unformed stools less than classic TD definition.

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Taylor 2006	Patients consulting travel health clinics in Mexico, Guatemala, India, or Peru, mean age=33yrs n=202	Ciprofloxacin 500mg twice daily for three days vs. placebo	5 days	Adverse events 0.96 (0.59, 1.56) Median time to last unformed stool: 1.89 (1.34, 2.65)	**Adverse events: included in analysis** **Other outcomes: included in review, excluded from analysis**
Ericsson 1987	U.S. college students in Mexico, mean age=28yrs n=127	Ciprofloxacin 500mg twice daily for five days vs. placebo	5 days	Duration of diarrhea N/A	**Included in review, excluded from analysis**
Wistrom 1992	U.S. volunteers in Mexico, mean age=34yrs n=42	Ciprofloxacin 250mg twice daily for three days vs. placebo	72 hours	Cure after 48hrs N/A Duration of diarrhea N/A Mean number of stools N/A	**Excluded from analysis** Very small study population and large exclusion (only 15 subjects evaluated for efficacy).
Salam 1994	British military personnel in Belize, age not given n=88	Ciprofloxacin 500mg, single dose vs. placebo	72 hours	Cured of TD at 72hrs: 1.21 (1.02, 1.44)	**Excluded from analysis** Number of unformed stools less than classic TD definition.
Azithromycin for the treatment of TD					
Kuschner 1995	U.S. military personnel in Thailand, mean age=30yrs n=79	Azithromycin 500mg once daily for three days vs. Ciprofloxacin 500mg once daily for three days	72 hours	Recovered by 24hrs: 0.70 (0.37, 1.35) Recovered by 48hrs: 1.02 (0.76, 1.37) Recovered by 72hrs: 1.06 (0.96, 1.16) Treatment failure: 1.26 (0.52, 3.07)	**Included in analysis**

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Adachi 2003	U.S. college students in Mexico, mean age=25yrs n=217	Azithromycin 1000mg, single dose vs. Levofloxacin 500mg, single dose	4 days	Immediate cure: 0.37 (0.17, 0.79) Treatment failure: 1.26 (0.52, 3.07)	**Included in analysis**
Sanders 2007	U.S. military and their beneficiaries in Turkey, median age=31yrs n=207	Azithromycin 1000mg, single dose plus loperamide vs. Levofloxacin 500mg, single dose plus loperamide	72 hours	Immediate cure: 0.76 (0.26, 1.99) Recovered by 24hrs: 0.82 (0.61, 1.11) Recovered by 48hrs: 1.41 (0.96, 2.07) Recovered by 72hrs: 0.95 (0.50, 1.80) Nausea immediately after first dose: 7.62 (0.97, 59.86) Vomiting immediately after first dose: 2.86 (0.12, 69.40) Nausea during remainder of follow-up: 0.94 (0.72, 1.31) Vomiting during remainder of follow-up: 0.70 (0.34, 1.45)	**Included in analysis**

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Tribble 2007	U.S. military personnel in Thailand, median age=26yrs n=156	Azithromycin 500mg once daily for three days or single dose vs. Levofloxacin 500mg once daily for three days	72 hours	Recovered by 24hrs: 0.70 (0.37, 1.35) Recovered by 48hrs: 1.02 (0.76, 1.37) Recovered by 72hrs: 1.06 (0.96, 1.16) Nausea immediately after first dose: 5.15 (0.68, 39.13) Vomiting immediately after first dose: 1.56 (0.06, 37.60) Nausea during remainder of follow-up: 2.02 (0.60, 6.84) Vomiting during remainder of follow-up: 1.29 (0.26, 6.41)	**Included in analysis**
Rifaximin for the treatment of TD					
Steffen 2003	Patients consulting travel health clinics in Mexico, Guatemala, or Kenya, mean age=29yrs n=380	Rifaximin 600mg, 200mg three times daily or 1200mg, 400mg three times daily for three days vs. placebo	5 days	Clinical cure after 5 days: 1.29 (1.15, 1.45) Treatment failure: 0.47 (0.33, 0.68) Adverse events: 0.93 (0.80, 1.07)	**Included in analysis**

AUTHOR/YEAR	STUDY POPULATION	TREATMENT AND DOSAGE/ COMPARISON	FOLLOW-UP	OUTCOME RELATIVE RISK (95%CI)	COMMENTS
Taylor 2006	Patients consulting travel health clinics in Mexico, Guatemala, India, or Peru, mean age=33yrs n=298	Rifaximin 600mg, 200mg three times daily for three days vs. placebo Rifaximin 600mg, 200mg three times daily for three days vs. Ciprofloxacin 1000mg, 500mg twice daily for three days	5 days	Clinical cure after 5 days: 1.25 (1.05, 1.48) Treatment failure: 0.55 (0.35, 0.88) Adverse events: 1.07 (0.71, 1.61) Clinical cure after 5 days: 0.98 (0.86, 1.11) Treatment failure: 1.80 (0.81, 4.02) Adverse events: 1.11 (0.73, 1.69)	**Included in analysis**
DuPont 2001	U.S. college students in Mexico and travellers to Jamaica, mean age=26yrs n=187	Rifaximin 800mg, 400mg twice daily for three days vs. Ciprofloxacin 1000mg, 500mg twice daily for three days	5 days	Clinical cure after 5 days: 0.99 (0.89, 1.10) Treatment failure: 1.82 (0.63, 5.22) Adverse events: 0.92 (0.62, 1.37)	**Included in analysis**

* studies are randomized, double-blind, placebo-controlled trials unless otherwise specified

TABLE 2: Dosages for various agents to prevent and treat travellers' diarrhea

AGENT	DOSAGE—CHEMOPROPHYLAXIS	DOSAGE—TREATMENT	COMMENTS
Antimotility agents			
Loperamide	N/A	**Adults:** 4 mg initially + 2 mg after each loose stool (16 mg daily maximum) **Children:** *First 24 hours:* 2–6 years (13–20kg): 1 mg, 3 times daily 6–8 years (20–30kg): 2 mg, twice daily 8–12 years (>30kg): 2 mg, 3 times daily *From 24–48 hours, after each loose stool:* 0.1 mg/kg (not to exceed initial dose)	Contraindicated in infants < 2 years of age
Antisecretory agents			
Bismuth subsalicylate	Two 262 mg tablets (524 mg), 4 times daily	**Adults:** 524–1048 mg every 30–60 minutes as needed (4.2 g maximum dose/24hrs) **Children:** Dose every 30–60 minutes as needed 2–4 years: 88–176 mg (0.7 g maximum dose/24hrs) 5–9 years: 131–262 mg (1.05 g maximum dose/24hrs) 10–14 years: 262–524 mg (2.1 g maximum dose/24hrs)	Chemoprophylaxis not recommended in children and treatment not recommended in infants < 2 years of age. Chemoprophylaxis should not exceed three weeks in adults. Treatment should not exceed 2 days in adults and children. Halving of the dose for chemoprophylaxis is a possible alternative if higher dosage not feasible. Treatment contraindicated in ASA allergy.

AGENT	DOSAGE—CHEMOPROPHYLAXIS	DOSAGE—TREATMENT	COMMENTS
Antibiotic agents			
Norfloxacin	400 mg, once daily	800 mg single dose 400 mg, twice daily for 3 days	**Fluoroquinolones:** Treatment contraindicated in pregnant women. Caution recommended for travellers to the Indian sub-continent and southeast Asia due to presence of antibiotic resistant pathogens. Risks for adverse events may be increased in children under the age of 18, and these risks should be balanced against the potential benefits.
Ciprofloxacin	500 mg, once daily	**Adults:** 500–1000 mg single dose 500 mg, twice daily for 3 days Treatment course need not be completed if symptoms resolve, and lower doses may be sufficient. **Children:** 20–30 mg/kg/day, divided, twice daily for 3 days (max 1.5 g/24 hours)	
Ofloxacin	300 mg, once daily	400 mg single dose 200 mg, twice daily for 3 days	
Levofloxacin	500 mg, once daily	1000 mg single dose 500 mg, once daily for 3 days	
Azithromycin	Children:	**Adults:** 1000 mg single dose 500 mg, once daily for 3 days **Children:** 5–10 mg/kg, once daily for 3 days (max 500 mg/24 hours)	Alternative for treatment for those travelling to regions with high quinolone resistance. Prevention of TD in children with azithromycin has not been studied, and should be used with caution.

AGENT	DOSAGE—CHEMOPROPHYLAXIS	DOSAGE—TREATMENT	COMMENTS
Rifaximin	600mg, once daily Lower doses, such as 200mg once or twice daily, have been used with variable effectiveness.	200mg, 3 times daily for 3 days	For prevention: only the 550mg tablet for Rifaximin (Zaxine) is market-approved in Canada. However, CATMAT considers this difference in dosage to not be clinically important. For treatment: 200mg tablets are not available in Canada. The manufacturer does not recommend splitting the 550mg tablets. 200mg tablets are approved for use in some other countries. Rifaximin has not been studied nor approved for use in children under the age of 12, nor has dosing in children been established.
Cefixime	N/A	400 mg single dose 8 mg/kg, once daily for 3 days	Alternative for children if quinolones and macrolides contraindicated. There are no clinical data for the use of cefixime in TD.

SOURCES: CPS (e-CPS, accessed November 8, 2013); 2001 CATMAT statement; additional details from GRADE assessment studies and; for children, from: Stauffer WM, Konop RJ, Kamat D. Traveling with infants and young children. part III: Travelers' diarrhea. Journal of travel medicine. 2002;9(3):141–50.

NOTES FROM THE CPS

- Loperamide (Imodium Caplets/Quick-Dissolve/Calming Liquid/Liqui-Gels):
- No dose adjustment required for the elderly
- Loperamide should only be used in children (2–12 years) on the advice of a physician. Liqui-Gels, caplets and Quick-Dissolve tablets are not suited for children under 6 years of age
- The use of Imodium in children under 2 years of age is contraindicated

BSS

- Do not use in second half of pregnancy
- Use with caution during breast-feeding
- Use with caution, if at all, in patients with renal impairment
- Do not use for self-medication in patients with ulcer, bleeding disorder or bloody or black stools

QUINOLONES

- In the past use of fluoroquinolones has been discouraged in children under 18 and, aside from cipro, their effects are poorly understood in pediatric population. However, there are also some potential benefits and more study is needed.
- Dosage information is given for cipro with caveat that use is generally restricted to very specific indications and is, ideally, monitored by an infectious disease specialist
- Adjust dosage for patients with renal impairment as per Tables 6–9 in CPS

TABLE 3: Preparing oral rehydration solutions at home

Homemade oral rehydration solution:

INGREDIENTS	AMOUNT
Purified water	1 L (4¼ cups)
Salt	2.5 mL (½ teaspoon)
Sugar	30 mL (6 teaspoons)

Dosage:

AGE	AMOUNT
Children under 2 years	50–100 mL (¼ to ½ cup) after each loose stool, up to approximately 0.5L (2 cups) a day.
Children 2 to 9 years	100–200 mL (½ to 1 cup) after each loose stool, up to approximately 1L (4¼ cups) a day.
Persons 10 years or older	As much as wanted, up to approximately 2L (8½ cups) a day.

SOURCE: Government of Canada (travel.gc.ca)

For more information visit: http://travel.gc.ca/travelling/health-safety/rehydration

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APPENDICES

APPENDIX 1
LITERATURE REVIEW SEARCH STRATEGY EXAMPLE

Dukoral

Scopus (TITLE-ABS-KEY(("Dukoral" OR "oral cholera" OR "WC/rBS" OR ("whole-cell" W/2 "recombinant B subunit") OR "BS-WC" OR "B-subunit/whole cell" OR " rBS-WC") AND (vaccine* OR immuni?ation*)) AND TITLE-ABS-KEY(travel* W/2 (diarrhoea OR diarrhea))) AND PUBYEAR > 1969 AND (LIMIT-TO(LANGUAGE, "English"))

Database(s): **Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R)** 1946 to Present

Search Strategy:

#	SEARCHES	RESULTS
1	*Cholera Vaccines/	867
2	Cholera Vaccines/	1308
3	(("Dukoral" or "oral cholera" or "WC/rBS" or ("whole-cell" adj2 "recombinant B subunit") or "BS-WC" or "B-subunit/whole cell" or " rBS-WC") and (vaccine* or immuni?ation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	332
4	(travel* adj2 (diarrhea or diarrhoea)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1295
5	1 or 2 or 3	1370
6	4 and 5	28

Database(s): Embase 1974 to 2013 May 16

Search Strategy:

#	SEARCHES	RESULTS
1	*Cholera Vaccines/	1412
2	Cholera Vaccines/	2548
3	(("Dukoral" or "oral cholera" or "WC/rBS" or ("whole-cell" adj2 "recombinant B subunit") or "BS-WC" or "B-subunit/whole cell" or " rBS-WC") and (vaccine* or immuni?ation*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	504
4	(travel* adj2 (diarrhea or diarrhoea)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3562
5	1 or 2 or 3	2588
6	traveller diarrhea/	1823
7	4 or 6	3562
8	5 and 7	204
9	cholera vaccine/	2548
10	cholera vaccine/	2548
11	3 or 10	2588
12	7 and 11	204
13	limit 12 to (english language and yr="1970 -Current")	162

Database(s): Global Health 1973 to 2013 Week 19

Search Strategy:

#	SEARCHES	RESULTS
1	(("Dukoral" or "oral cholera" or "WC/rBS" or ("whole-cell" adj2 "recombinant B subunit") or "BS-WC" or "B-subunit/whole cell" or " rBS-WC") and (vaccine* or immuni?ation*)).mp. [mp=abstract, title, original title, broad terms, heading words]	206
2	(travel* adj2 (diarrhea or diarrhoea)).mp. [mp=abstract, title, original title, broad terms, heading words]	755
3	travellers' diarrhoea/	117
4	2 or 3	755
5	1 and 4	12
6	limit 5 to (english language and yr="1970 -Current")	12

APPENDIX 2
GRADE TABLES FOR EACH TD INTERVENTION

1. **Vaccine for <u>prevention</u> of travellers' diarrhea**

Oral inactivated cholera vaccine (WC-BS and WC-rCTB) versus non-vaccinated for prevention of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cholera vaccine (WC-BS and WC-rCTB)	Non-vaccinated (RCT only)	Relative (95% CI)	Absolute		
Episode of travellers' diarrhea (follow-up 0–35 days; assessed with: Patient self-assessment and clinical follow-up)												
3[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency[3]	serious[4]	no serious imprecision	none	216/616 (35.1%)	232/626 (37.1%)	**RR* 0.94 (0.82 to 1.09)**	22 fewer per 1000 (from 67 fewer to 33 more)	●●●○ MODERATE	CRITICAL

* RR = relative risk

STUDIES: Peltola 1991, Scerpella 1995, Wiedermann 2000

[1] Five observational studies (Lopez-Gigosos 2007, 2009, 2013, Torrell 2009, Gabutti 2012) were excluded due to low quality of study design. One RCT study (Clemens 1988) was excluded as it was not conducted in a traveller population.

[2] Although one study did not clearly state loss to follow-up and one other had 21% loss to follow-up, these were not deemed sufficient to rate down for quality.

[3] Although I^2 value is high, all three RCTs include the null, all 95%CIs overlap and test for heterogeneity is non-significant.

[4] Due to heterogeneity in type of vaccine, vaccine administration & definitions used for TD.

2. **Bismuth subsalicylate (BSS) for <u>prevention</u> of travellers' diarrhea**

Bismuth subsalicylate (BSS) versus Placebo for prevention of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bismuth subsalicylate (BSS)	Placebo	Relative (95% CI)	Absolute		
Episode of travellers' diarrhea during follow-up (follow-up 0–30 days; assessed with: Patient self-assessment)												
3[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	105/335 (31.3%)	109/196 (55.6%)	**RR 0.55 (0.44 to 0.67)**	250 fewer per 1000 (from 184 fewer to 311 fewer)	●●●● HIGH	CRITICAL

STUDIES: DuPont 1980, Steffen 1986, DuPont 1987.

[1] One study (Graham 1983) was excluded due to inadequate definition of TD.

[2] Although one of the studies had a large loss to follow-up, when it is removed, the effect remains strong and becomes more consistent.

[3] Although the I^2 values are high, the studies all show a strong protective effect and 95%CIs all overlap with each other.

High dose BSS (2.1 g–4.2 g per day) versus Placebo for prevention of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose BSS (2.1–4.2g per day)	Placebo	Relative (95% CI)	Absolute		
Episode of travellers' diarrhea during follow-up (follow-up 0–30 days; assessed with: Patient self-assessment)												
3[1]	randomised trials	no serious risk of bias[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	59/201 (29.4%)	109/196 (55.6%)	**RR 0.51 (0.39 to 0.65)**	272 fewer per 1000 (from 195 fewer to 339 fewer)	●●●● HIGH	CRITICAL

STUDIES: DuPont 1980, Steffen 1986, DuPont 1987.

[1] One study (Graham 1983) was excluded due to inadequate definition of TD.

[2] Although one of the studies had a large loss to follow-up, when it is removed, the effect remains strong and becomes more consistent.

[3] Although the I^2 values are high, the studies all show a strong protective effect and 95%CIs all overlap with each other.

Low dose BSS (1.05 g per day) versus Placebo for prevention of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose BSS (1.05g per day)	Placebo	Relative (95% CI)	Absolute		
Episode of travellers' diarrhea during follow-up (follow-up 0–30 days; assessed with: Patient self-assessment)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46/134 (34.3%)	69/130 (53.1%)	**RR 0.65 (0.50 to 0.86)**	186 fewer per 1000 (from 74 fewer to 265 fewer)	●●○○ LOW	CRITICAL

STUDIES: Steffen 1986, DuPont 1987.

[1] One of the two studies had a large loss to follow-up.

[2] Insufficient sample size and number of events.

High dose BSS (2.1 g–4.2 g per day) versus Low dose BSS (1.05 g per day) for prevention of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose BSS (2.1-4.2 g per day)	Low dose BSS (1.05 g per day)	Relative (95% CI)	Absolute		
Episode of travellers' diarrhea during follow-up (follow-up 0–30 days; assessed with: Patient self-assessment)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/139 (32.4%)	46/134 (34.3%)	**RR 0.87 (0.63 to 1.22)**	45 fewer per 1000 (from 127 fewer to 76 more)	●●○○ LOW	CRITICAL

STUDIES: Steffen 1986, DuPont 1987.

[1] One of the two studies had a large loss to follow-up.

[2] Insufficient sample size and number of events.

3. **Fluoroquinolones for <u>prevention</u> of travellers' diarrhea**

Fluoroquinolones versus Placebo for prevention of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolones	Placebo	Relative (95% CI)	Absolute		
Episode of travellers' diarrhea during follow-up (follow-up 5–21 days; assessed with: Patient self-assessment)												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	13/316 (4.1%)	109/327 (33.3%)	**RR 0.12 (0.07 to 0.21)**	293 fewer per 1000 (from 263 fewer to 310 fewer)	●●●● HIGH	CRITICAL

STUDIES: 1) Norfloxacin (n=3): Johnson 1986, Wiström 1987, Scott 1990; 2) Ciprofloxacin (n=1): Heck 1994

[1] One study (Rademaker 1989) was excluded due to inadequate definition of TD.

[2] Insufficient Optimal Information Size (OIS): number of events recommended by GRADE authors to achieve a RR reduction of 25%, given alpha=0.05 & beta=0.2 is 250 vs. 122 observed. However, all point estimates show a large, significant protective effect.

4. **Rifaximin for <u>prevention</u> of travellers' diarrhea**

Rifaximin versus placebo for prevention of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rifaximin	Placebo	Relative (95% CI)	Absolute		
Occurrence of travellers' diarrhea (combined tx arms DuPont 2005) (follow-up 0–26 days; assessed with: Patient self-assessment and clincial follow-up)												
5	randomised trials	no serious risk of bias	no serious inconsistency[1]	no serious indirectness[2]	no serious imprecision	reporting bias[3]	74/475 (15.6%)	135/368 (36.7%)	**RR 0.42 (0.33 to 0.53)**	213 fewer per 1000 (from 172 fewer to 246 fewer)	●●●○ MODERATE	CRITICAL

STUDIES: DuPont 2005 (all 3 treatment arms combined), Armstrong 2010, Martinez-Sandoval 2010, Flores 2011, Zanger 2013.

[1] Although the I^2 values are high, all studies show a consistent protective effect for rifaximin and all 95%CIs overlap.

[2] Dosage varies between studies. However, estimates change very little when only 550mg–600mg dosage results are considered.

[3] One large (n=660) unpublished study completed in 2008 was found on ClinicalTrials.gov database: no results reported. Studies are all of small or moderate size.

5. **Loperamide for <u>treatment</u> of travellers' diarrhea**

Loperamide versus placebo for treatment of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loperamide	Placebo	Relative (95% CI)	Absolute		
Number of loose stools during first day of treatment (follow-up 0–5 days; measured with: Patient diary and clinical follow-up; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	65	67	—	MD 1.59 lower (2.92 to 0.26 lower)	●●○○ LOW	CRITICAL
First relief of acute diarrhea after 4 hours of treatment (follow-up 0–3 days; assessed with: Patient diary)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	55/155 (35.5%)	33/157 (21%)	**RR 1.69 (1.17 to 2.45)**	145 more per 1000 (from 36 more to 305 more)	●●○○ LOW	CRITICAL
First relief of acute diarrhea after 12 hours of treatment (follow-up 0–3 days; assessed with: Patient diary)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[4]	none	74/155 (47.7%)	50/157 (31.8%)	**RR 1.50 (1.13 to 1.99)**	159 more per 1000 (from 41 more to 315 more)	●●○○ LOW	CRITICAL
First relief of acute diarrhea after 24 hours of treatment (follow-up 0–3 days; assessed with: Patient diary)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision[5]	none	108/155 (69.7%)	79/157 (50.3%)	**RR 1.38 (1.15 to 1.66)**	191 more per 1000 (from 75 more to 332 more)	●●●○ MODERATE	CRITICAL

* MD = mean difference

STUDIES: 1) Number of loose stools: Bergstrom 1986, van Loon 1989; 2) First relief of acute diarrhea: Hughes 1995, van den Eynden 1995

[1] One of the two studies does not use a traveller study population. One of the studies did not specify if stools were unformed.

[2] Standard errors used to calculate 95%CIs were approximated from graphical representations (van Loon) or were derived from median and range data (Bergstrom) and as such, may not be precise. Insufficient sample size and number of events. Both studies have 95%CIs which include the null.

[3] Both studies did not use a traveller study population.

[4] Insufficient sample size and number of events (OIS).

[5] Number of events and sample size is borderline acceptable. However, both studies have 95%CIs which do not include the null.

Loperamide and antibiotic versus antibiotic alone for treatment of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loperamide and antibiotic	Antibiotic alone	Relative (95% CI)	Absolute		
Complete relief of TD after 24hrs (follow-up 0–5 days; assessed with: Patient assessment with clinical follow-up)												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision	none	143/254 (56.3%)	92/253 (36.4%)	**RR 1.55 (1.28 to 1.86)**	200 more per 1000 (from 102 more to 313 more)	●●●● HIGH	CRITICAL
Complete relief of TD after 48hrs (follow-up 0–5 days; assessed with: Patient assessment with clinical follow-up)												
4[1]	randomised trials	no serious risk of bias	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision	none	186/254 (73.2%)	150/253 (59.3%)	**RR 1.24 (1.09 to 1.40)**	142 more per 1000 (from 53 more to 237 more)	●●●● HIGH	CRITICAL
Complete relief of TD after 72hrs (follow-up 0–5 days; assessed with: Patient assessment with clinical follow-up)												
4	randomised trials	no serious risk of bias	serious[4]	no serious indirectness[3]	no serious imprecision	none	212/254 (83.5%)	196/255 (76.9%)	**RR 1.09 (1.00 to 1.19)**	69 more per 1000 (from 0 more to 146 more)	●●●○ MODERATE	CRITICAL
Treatment failure (follow-up 0–5 days; assessed with: Patient assessment with clinical follow-up)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[5]	serious[6]	none	3/142 (2.1%)	19/144 (13.2%)	**RR 0.18 (0.06 to 0.55)**	108 fewer per 1000 (from 59 fewer to 124 fewer)	●●●○ MODERATE	CRITICAL

STUDIES: 1) Complete relief at 24hrs, 48hrs and 72hrs: Petruccelli 1992, Ericsson 1990, 2007, DuPont 2007; 2) Treatment failure: Ericsson 1990, 1997, 2007

[1] One study (Taylor 1991) was excluded due to inadequate TD definition.

[2] Although the I^2 values are high, 95%CIs from all studies overlap and magnitude of effect is relatively consistent.

[3] Although one study had a different definition of outcome (included improvement), this was not judged sufficient to downgrade.

[4] Substantial variation in direction of effect, 95%CIs do not all overlap, high I^2.

[5] Although all the studies were conducted in the same population, this was not judged as sufficient to downgrade.

[6] Insufficient number of subjects and events to detect effect (OIS). Two of three studies have extremely wide 95%CIs which include null.

6. **Fluoroquinolones for the <u>treatment</u> of travellers' diarrhea**

Fluoroquinolones versus placebo for treatment of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolones versus placebo	Control	Relative (95% CI)	Absolute		
Cured of TD at 72 hours (follow-up 0–3 days; assessed with: Patient assessment and some clinical follow-up)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	70/97 (72.2%)	41/103 (39.8%)	**RR 1.81 (1.39 to 2.37)**	322 more per 1000 (from 155 more to 545 more)	●●●○ MODERATE	CRITICAL
Adverse events (follow-up 0–5 days; assessed with: Patient assessment and some clinical follow-up)												
3	randomised trials	no serious risk of bias	serious[3]	serious[4]	serious[2]	none	109/378 (28.8%)	50/243 (20.6%)	**RR 1.39 (1.05 to 1.83)**	80 more per 1000 (from 10 more to 171 more)	●○○○ VERY LOW	CRITICAL

STUDIES: 1) Cured at 72hrs: Wiström 1989 (norfloxacin), Mattila 1993 (norfloxacin); 2) Adverse events: DuPont 1992 (ofloxacin), Steffen 1993 (fleroxacin), Taylor 2006 (ciprofloxacin)

[1] Two studies (Salam 1994 and Steffen 1993) were excluded from analysis since they had an inadequate definition of traveller's diarrhea (1+ unformed stools).

[2] Number of events and sample size probably insufficient to detect effect (according to Optimal Information Size criteria).

[3] Differing direction of effect across studies. Large I^2 value observed.

[4] Lack of standardized criteria across studies for definition of what constitutes an adverse effect.

7. **Azithromycin for the <u>treatment</u> of travellers' diarrhea**

Azithromycin versus fluoroquinolones for treatment of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Fluoroquinolones	Relative (95% CI)	Absolute		
Rapid/immediate cure (follow-up 0–4 days; assessed with: Patient self-assessment and some clinical follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	14/211 (6.6%)	30/207 (14.5%)	**RR 0.46 (0.25 to 0.84)**	78 fewer per 1000 (from 23 fewer to 109 fewer)	●●○○ LOW	CRITICAL
Treatment failure (follow-up 0–4 days; assessed with: Patient self-assessment and clinical follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency[3]	serious[4]	serious[5]	none	10/140 (7.1%)	10/143 (7%)	**RR 1.02 (0.45 to 2.32)**	1 more per 1000 (from 38 fewer to 92 more)	●●○○ LOW	CRITICAL
Recovered by 24hr (follow-up 0–3 days; assessed with: Patient self-assessment and some clinical follow-up)												
3	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	serious[7]	none	73/244 (29.9%)	79/191 (41.4%)	**RR 0.79 (0.61 to 1.01)**	87 fewer per 1000 (from 161 fewer to 4 more)	●●○○ LOW	CRITICAL
Recovered by 48hr (follow-up 0–3 days; assessed with: Patient self-assessment and some clinical follow-up)												
3	randomised trials	no serious risk of bias	serious[8]	serious[6]	no serious imprecision	none	129/244 (52.9%)	75/191 (39.3%)	**RR 1.34 (1.08 to 1.66)**	134 more per 1000 (from 31 more to 259 more)	●●○○ LOW	CRITICAL
Recovered by 72hr (follow-up 0–3 days; assessed with: Patient self-assessment and some clinical follow-up)												
3	randomised trials	no serious risk of bias	serious[8]	serious[6]	no serious imprecision	none	144/244 (59%)	88/191 (46.1%)	**RR 1.16 (1.00 to 1.33)**	74 more per 1000 (from 0 more to 152 more)	●●○○ LOW	CRITICAL

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Fluoroquinolones	Relative (95% CI)	Absolute		
Nausea immediately after first dose (30 min) (follow-up 0–3 days; assessed with: Clinical observation)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	serious[7]	none	18/209 (8.6%)	2/154 (1.3%)	**RR 6.23 (1.48 to 26.26)**	68 more per 1000 (from 6 more to 328 more)	●●○○ LOW	IMPORTANT
Vomiting immediately after first dose (30 min) (follow-up 0–3 days; assessed with: Patient self-assessment and some clinical follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	serious[7]	none	2/209 (0.96%)	0/154 (0%)	**RR 2.13 (0.23 to 19.75)**	—	●●○○ LOW	IMPORTANT
Nausea (starting after tx) during remainder of 3-day observation period (follow-up 0–3 days; assessed with: Patient self-assessment and some clinical follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	no serious imprecision	none	65/209 (31.1%)	57/153 (37.3%)	**RR 1.01 (0.77 to 1.31)**	4 more per 1000 (from 86 fewer to 115 more)	●●●○ MODERATE	IMPORTANT
Vomiting (starting after tx) during remainder of 3-day observation period (follow-up 0–3 days; assessed with: Patient self-assessment and some clinical follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[6]	serious[9]	none	16/209 (7.7%)	17/154 (11%)	**RR 0.78 (0.41 to 1.52)**	24 fewer per 1000 (from 65 fewer to 57 more)	●●○○ LOW	NOT IMPORTANT

STUDIES: 1) Rapid cure: Adachi 2003, Sanders 2007; 2) Treatment failure: Kuschner 1995, Adachi 2003; 3) Recovered by 24hrs, 48hrs, 72hrs: Adachi 2003, Sanders 2007, Tribble 2007; 4) Adverse events (nausea and vomiting): Sanders 2007, Tribble 2007

[1] One study includes loperamide use in its dosage whereas the other does not.

[2] One of the two studies has a 95%CI which includes large benefit and large risk. Number of events and sample size most likely insufficient to detect effect (OIS).

[3] Although the estimates show opposing effects, the 95%CIs both include the null and I^2 is low.

[4] Study locations differ with respect to Campylobacter prevalence. Also differing dosages for treatment.

[5] 95%CIs for both studies include large benefit and large risk. Insufficient sample size and number of events to detect effect (OIS).

[6] One study includes loperamide use in its dosage whereas the other does not. Study locations differ with respect to Campylobacter prevalence. Also differing dosages for treatment.

[7] All studies have a 95%CI which includes large benefit and the null. Number of events and sample size most likely insufficient to detect effect (OIS).

[8] Not all studies have 95%CIs overlapping null. Relatively high I^2.

[9] All studies have 95%CIs which include substantial benefit and harm. Number of events and sample size most likely insufficient to detect effect (OIS).

8. **Rifaximin for the <u>treatment</u> of travellers' diarrhea**

Rifaximin versus placebo for treatment of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rifaximin	Placebo	Relative (95% CI)	Absolute		
Wellness after 120 hours of follow-up (follow-up 0–5 days; assessed with: Patient self-assessment with clinical follow-up[1])												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	335/427 (78.5%)	134/220 (60.9%)	**RR 1.29 (1.15 to 1.45)**	177 more per 1000 (from 91 more to 274 more)	●●●● HIGH	CRITICAL
Treatment failure (follow-up 0–5 days; assessed with: Patient self-assessment with clinical follow-up[3])												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	70/427 (16.4%)	72/220 (32.7%)	**RR 0.50 (0.38 to 0.67)**	164 fewer per 1000 (from 108 fewer to 203 fewer)	●●●● HIGH	CRITICAL
Adverse events (follow-up 0–5 days; assessed with: Patient self-assessment with clinical follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	215/450 (47.8%)	115/229 (50.2%)	**RR 0.96 (0.83 to 1.11)**	20 fewer per 1000 (from 85 fewer to 55 more)	●●●● HIGH	CRITICAL

STUDIES: Steffen 2003, Taylor 2006.

[1] Wellness is defined as 48hrs with no unformed stool and no fever, or 24hrs without watery stools, maximum two soft stools, and no clinical symptoms after 120hrs of follow-up from first dose.

[2] Although there were differences in dosage for treatment, effect did not appreciably change when limited to 600mg dosage.

[3] Treatment failure is defined as clinical deterioration or worsening of symptoms after at least 24hrs of therapy or illness continuing after 120 hrs of treatment with study medication or after at least 24hrs of therapy.

Rifaximin versus ciprofloxacin for treatment of travellers' diarrhea

QUALITY ASSESSMENT							No. OF PATIENTS		EFFECT		QUALITY	IMPORTANCE
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rifaximin	Ciprofloxacin	Relative (95% CI)	Absolute		
Wellness after 120 hours of follow-up (follow-up 0–5 days; assessed with: Patient self-assessment with clinical follow-up[1])												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	232/290 (80%)	162/195 (83.1%)	**RR 0.98 (0.90 to 1.07)**	17 fewer per 1000 (from 83 fewer to 58 more)	●●●● HIGH	CRITICAL
Treatment failure (follow-up 0–5 days; assessed with: Patient self-assessment with clinical follow-up[3])												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	serious[4]	none	34/279 (12.2%)	12/188 (6.4%)	**RR 1.81 (0.96 to 3.43)**	52 more per 1000 (from 3 fewer to 155 more)	●●●○ MODERATE	CRITICAL
Adverse events (follow-up 0–5 days; assessed with: Patient self-assessment with clinical follow-up)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	84/292 (28.8%)	58/194 (29.9%)	**RR 1.01 (0.76 to 1.35)**	3 more per 1000 (from 72 fewer to 105 more)	●●●● HIGH	CRITICAL

STUDIES: DuPont 2001, Taylor 2006.

[1] Wellness is defined as 48hrs with no unformed stool and no fever, or 24hrs without watery stools, maximum two soft stools, and no clinical symptoms after 120hrs of follow-up from first dose.

[2] Although treatment dosages differ (rifaximin 600mg vs. 800mg), these differences were considered to be minimal.

[3] Treatment failure is defined as clinical deterioration or worsening of symptoms after at least 24hrs of therapy or illness continuing after 120hrs of treatment with study medication or after at least 24hrs of therapy.

[4] Both studies have wide 95%CIs which include large harm and benefit. There are most likely an insufficient sample size and number of events to detect effect.