

## Inside this issue: Typhoid

There are four Typhoid vaccines approved for use in Canada. Find out the latest recommendations for their use in the summary of a recent statement by the Committee to Advise on Tropical Medicine and Travel (CATMAT). And learn more about GRADE - Grading of Recommendations Assessment, Development and Evaluation – a methodology increasingly adopted by Advisory Committees to inform the development of questions and assessment of, assess evidence, and make transparent the values and evidence underlying the recommendations.

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### Useful link

Travel Health Fact Sheet: Typhoid Fever

<http://travel.gc.ca/travelling/health-safety/diseases/typhoid>

Statement on International Travellers and Typhoid

<http://publications.gc.ca/site/eng/460371/publication.html>



## Summary of the *Statement on International Travellers and Typhoid* by the Committee to Advise on Tropical Medicine and Travel (CATMAT)

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### Abstract

**Background:** Typhoid fever is an enteric febrile illness with symptoms that range from mild to potentially fatal. Among Canadians it is usually acquired during travel to typhoid endemic countries. The Committee to Advise on Tropical Medicine and Travel (CATMAT) assembled a typhoid working group to update recommendations on typhoid and international travel. This document is a summary of the new typhoid statement.

**Methods:** Following a systematic review of the literature, typhoid vaccine recommendations were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate data quality, benefits and harms, and values and preferences. The literature search focused on systematic reviews of typhoid vaccine efficacy and identified studies of disease burden, pathogenesis, risk factors and prevention. Other recommendations were based on a review of the retrieved literature and expert opinion.

**Results:** Typhoid vaccine is moderately effective (~50%), well tolerated, with very low risk of serious adverse events. Studies of typhoid vaccine efficacy, morbidity or mortality among travellers were not found, although studies on populations in typhoid endemic countries were identified. Among travellers, destination of travel is the strongest and most consistent typhoid risk predictor; the highest risk was for travel to South Asia. Confidence in effect estimates for other potential risk factors was very low.

**Recommendations:** CATMAT suggests that typhoid vaccine (Ty21a or Vi polysaccharide vaccine) be used for most Canadian travellers visiting South Asia and not used for most Canadian travellers visiting destinations other than South Asia. The recommendations are conditional, due to the moderate confidence in the effect estimate. For destinations other than South Asia, providers should discuss risks and vaccine benefits and harms with the traveller as well as recommend basic hygiene precautions.

### Introduction

Typhoid fever is an enteric febrile illness caused by *Salmonella enterica* subsp. *enterica* serovars Typhi (*S. typhi*) (1;2). Humans are the only reservoir for this disease and exposure to the causative pathogen is usually through ingestion of water or food that has been contaminated by feces from an ill individual or a chronic carrier (3;4). Prevention involves vaccination, personal hygiene and food and water precautions.

The World Health Organization (WHO) estimates 21 million typhoid cases and 210,000 to 840,000 deaths annually worldwide (5;6). In endemic countries, widespread transmission is facilitated by poorly developed sanitation infrastructure (7). Most cases and deaths (more than 90%) occur in Asian countries, predominantly in South Asia (5). Incidence in high income countries is low (e.g., <15/100,000 persons per year) (1;3;8) and usually acquired during travel (9-12).

The clinical course of typhoid ranges from mild illness (low-grade fever) to severe systemic potentially fatal disease (2;3). The case fatality rate is approximately 10% for untreated cases in low income settings and <1% for patients receiving care in high income countries (13-17).

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada with ongoing and timely medical, scientific, and public health advice relating to tropical infectious disease and health risks associated with international travel. This is a summary of the CATMAT *Statement on International Travellers and Typhoid* where a full description of the evidence and recommendations is available (18).

## Methods

This is the first CATMAT statement to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to develop recommendations (19). GRADE is a new method of grading the quality of the evidence and strength of recommendations in guidelines used by many international organizations.

### Literature search and identification

An analytic framework identifying clinical preventive actions (interventions) for typhoid and risk factors for typhoid disease was developed. Key questions to define the magnitude of benefits and harms were identified as well as the following key “PICO” (population of interest, intervention, comparison and outcome) question:

***Among Canadian travellers, does the administration of typhoid vaccine versus no vaccine decrease the incidence of typhoid and the associated morbidity and mortality?***

Two types of typhoid vaccine are licensed in Canada, a live oral vaccine (Ty21a), and injectable Vi polysaccharide vaccines (**Table 1**). Only evidence for these types of vaccines was reviewed.

Relevant literature was identified by searching Ovid MEDLINE and Embase electronic databases using the terms “typhoid fever” and “travel”. The search spanned publications from January 1, 2000 to August 14, 2012. In addition, the Cochrane Database of Systematic Reviews was searched using the term “typhoid” from the start of the database up to and including July 2012. For all searches, only English and/or French articles were retained.

Systematic reviews that addressed the efficacy of typhoid vaccine were specifically sought. Studies that addressed burden of disease (incidence, morbidity, mortality, hospitalizations), especially for travellers; disease pathogenesis; population-specific risk factors (e.g., age, travellers visiting friends and relatives (VFR)); itinerary-specific risk factors (e.g., destination, duration of travel); efficacy of preventive measures (e.g., sanitation and hygiene); and/or disease treatment/management were also identified.

**Table 1: Typhoid vaccines licensed for use in Canada**

Vaccine	Parenteral, capsular polysaccharide vaccines (Typh-I)	Oral, live attenuated vaccine (Typh-O)	Combined vaccine
<b>Brand Name</b>	Typhim Vi® (20) (Sanofi Pasteur) TYPHERIX® (21) (GlaxoSmithKline Inc)	Vivotif® (capsules) (22) (CruceIl Switzerland Ltd)	ViVAXIM® (23) (Sanofi Pasteur) (combination of purified Vi polysaccharide typhoid with inactivated hepatitis A)
<b>Authorized for use in persons</b>	> 2 years of age	adults and children > 5 years of age	≥16 years of age
<b>Protection begins</b>	14 days following vaccination	7 days following vaccination	14 days following vaccination
<b>Dosage</b>	0.5 ml	4 enteric-coated capsules taken on alternate days	1.0 ml
<b>Route</b>	Single intramuscular injection	Orally in a series of doses	Single intramuscular injection
<b>Contraindications</b>	A severe local or systemic reaction to a previous dose of the vaccine	Individuals with hypersensitivity to any component of the vaccine or the enteric-coated capsule. Persons with an acute gastrointestinal condition or inflammatory bowel disease. Vaccine should not be administered to persons deficient in their ability to mount a humoral or cell-mediated response due to either a congenital or acquired immunodeficient state including treatment with immunosuppressive or antimetabolic drugs.	Known systemic hypersensitivity reaction to any component of ViVAXIM® or a life-threatening reaction after previous administration of the vaccine or a vaccine containing one or more of the same components
<b>Drug Interactions</b>	There are no known interactions	Antibiotics: Ty21a vaccination should be completed 3 days before commencing treatment with sulfonamides or other antibiotics. Antibiotic exceptions: Chloroquine, Mefloquine and Malarone do not influence the immune response of Ty21A and can be administered at any interval. When using any other antimalarial, immunization with Vivotif® should precede antimalarial prophylaxis using the 3 day interval.	
<b>Adverse Events</b>	Typhim Vi®: Pain at injection site, edema, redness, headache and malaise (20) TYPHERIX®: Pain at injection site, fever, headache, general aches, malaise, nausea and	Adverse reactions are infrequent and mild; nausea, abdominal pain, headache, fever, diarrhea, vomiting and skin rash.	ViVAXIM® Pain, edema or erythema at the injection site, myalgia, headache, fever, malaise, nausea and diarrhea (23).

Vaccine	Parenteral, capsular polysaccharide vaccines (Typh-I)	Oral, live attenuated vaccine (Typh-O)	Combined vaccine
	itching. These mild reactions occur in less than 10% of individuals vaccinated (21).		
<b>Efficacy with immunosuppression</b>	Immunocompromised persons (whether from disease or treatment) may not obtain the expected immune response.		
<b>Revaccination<sup>a</sup></b>	TyphimVi – every 3 years TYPHERIX <sup>®</sup> - every 3 years	Vivotif <sup>®</sup> - every 7 years <sup>b</sup>	Hepatitis A - Boost with a single dose of inactivated hepatitis A vaccine 6-36 months later for long term protection.  Typhoid - Revaccination with a single dose of purified Vi polysaccharide vaccine can be given at an interval of not more than 3 years.
<b>Interchangeability</b>	Although there are no data regarding the interchangeability of typhoid vaccines, it is presumed that re-immunization can be performed with any of the available formulations regardless of the vaccine used initially.		
<b>Safety in Pregnancy</b>	Safety in pregnancy has not been studied for any of the typhoid vaccines. Therefore, the benefits of vaccination must be carefully weighed against potential adverse events before it is given to pregnant women. Vaccine should only be used in pregnancy when there is a high risk of infection. There is no expected effect with purified polysaccharide vaccines.		

Sources: (20-23)

<sup>a</sup>Revaccination should be carried out when subjects remain at risk in conditions of repeated or continuous exposure. The Cochrane review presented data that sero protection continues for up to three years after immunization in endemic populations; there are data to indicate that protection from Ty21a extends to 7 years (24). There are no data on continued protection in travellers.

<sup>b</sup>CATMAT is aware that The Yellow Book - CDC Health Information for International Travellers 2012 advises repeat immunization with oral live attenuated Ty21a vaccine every 5 years however the CATMAT statement is consistent with the Health Canada Biologics and Genetic Therapies Directorate vaccine approval for re-immunization every 7 years.

## Assessment of evidence

Full details on GRADE methodology are described elsewhere (25). Briefly, the GRADE approach rates the quality of the evidence for specific clinical outcomes across studies, not study by study, by addressing flaws in methodology, consistency and generalizability of results and demonstrated effectiveness of the treatment (26;27). The GRADE approach takes into consideration the balance of benefits (efficacy) and harms of typhoid vaccine, the confidence in the estimates of effect for vaccination (high, moderate, low or very low), and what is believed to be the values and preferences of the traveller. GRADE quality assessments of studies of typhoid vaccine efficacy, vaccine adverse events and typhoid risk by destination region were performed, and results were collated into evidence profile and summary of findings tables (18).

In this statement, recommendations are expressed as strong or conditional as outlined in the **Appendix**. Other recommendations, not using the GRADE approach, do not use this terminology. These recommendations were based on evaluation of the relevant literature and expert opinion.

## Results

In total, 147 articles met the language and relevancy criteria and were included. Two additional studies on baseline risk (28;29) were identified after the initial literature review.

### Vaccine efficacy

No studies that addressed efficacy of typhoid vaccine in travellers or associated reductions in morbidity and mortality for this population were found. All included vaccine efficacy studies were conducted in populations living in typhoid endemic countries. A 2006 Cochrane Collaboration systematic review assessed 17 randomized or quasi-randomized trials (30) of typhoid vaccine among residents of endemic areas. An additional three randomized or quasi-randomized controlled clinical trials published after this systematic review were also identified and included in this analysis (31-33).

Expressed as three year cumulative risk of typhoid, persons receiving typhoid vaccine (Ty21a or Vi polysaccharide) were significantly less likely to develop typhoid fever than those who did not (Relative Risk (RR), 95% CI =0.51 (0.42 to 0.62)). For the same outcome, but measured as a two year cumulative risk of typhoid, RR was lower at 0.43 (0.34 to 0.54). Expressed by vaccine type, estimates ranged from RR=0.34 (0.19 to 0.60) for Ty21a after two years of follow-up to 0.53 (0.43 to 0.54) for Ty 21a after three years of follow-up; efficacy of Vi polysaccharide vaccine was intermediate to these values. Vaccine efficacy for different age groups was assessed separately by vaccine type as results were reported with different age stratifications. For both types of vaccine, the RR estimate was lower in older than in younger persons. However, these differences were not significant.

Estimates of effect were without serious risk of bias; but were rated down for indirectness as they only included residents of endemic areas (not travellers) and often were limited to younger age groups. There was moderate confidence in the estimate of effect for vaccine efficacy. No data on the impact of typhoid vaccination on morbidity and mortality were found.

### Adverse events associated with vaccine

Based on clinical trial data, adverse events (AE) associated with typhoid vaccines are generally mild and not significantly different from controls for: fever, vomiting, diarrhea, headaches, rash, or erythema. With Vi polysaccharide, pain at the injection site was more common among the vaccine recipients (RR=3.68; (1.96 to 6.93)). For enteric coated Ty21a, there was increased risk of: any mild adverse event (RR=1.78; (1.08 to 2.95)) (30) and nausea or abdominal pain (RR=2.13; (1.33 to 3.41)). Based on these data, it was estimated that there would be one additional AE due to pain for every 13 persons receiving Vi polysaccharide vaccine; and one mild AE and one nausea and abdominal pain AE for every 18 and 31 persons, respectively, receiving Ty21a.

### Risk factors

The strongest and most consistent predictor of typhoid risk in travellers is destination of travel. The estimated risk of developing travel associated typhoid is about: 1/3,000 travellers for travel to the South Asia (high risk), 1/50,000-100,000 for travel to Sub-Saharan Africa, North Africa and the Middle East, or South America (intermediate risk), and < 1/300,000 for travel to the Caribbean and Central America (low risk). South Asia is defined as Afghanistan, Bangladesh, Bhutan, India, Nepal, Maldives, Pakistan, and Sri Lanka. Among these countries, the large majority ( $\geq 90\%$ ) of cases of typhoid among travellers were reported from India, Pakistan and Bangladesh.

The confidence in the baseline estimates of typhoid risk by destination was reduced from high to moderate because of risk of bias due to possible under-ascertainment of cases and imprecision (i.e. unable to calculate confidence intervals due to incomplete stratified denominator data).

Several studies have identified other factors that increase the risk of travel associated typhoid, including travelling children, those visiting friends and relatives (VFRs), the presence of achlorhydria or use of acid suppression

therapy and longer duration of travel. The incremental magnitude of risk that these factors contribute in addition to travel destination is unclear.

## Values and preferences

There is evidence that typhoid vaccine is cost effective for residents of some endemic areas (34;35). However, cumulative risk is much higher among resident populations, and it is not appropriate to extrapolate cost-effectiveness to travellers paying for their own vaccine. No studies on traveller values and preferences or “Willingness to Pay” for typhoid (36) or other travel-related immunizations were identified. In the absence of data, it was estimated that the majority of Canadian travellers would consider typhoid vaccine use worth the cost and inconvenience where the risk of typhoid is estimated to be greater than 1 in 10,000 travellers, although at the individual level this decision may be influenced by other risk factors.

## Antimicrobials

The WHO considers fluoroquinolones to be the first line agents for typhoid treatment (37;38). In a 2011 Cochrane review, fluoroquinolones were found to result in fewer clinical failures compared to chloramphenicol, co-trimoxazole, amoxicillin and ampicillin (37). When the performance of quinolones was compared to other agents including cephalosporins (ceftriaxone and cefixime) or azithromycin, clinical outcomes appeared to be equivalent in most studies. Definitive conclusions could not be made as most of the data came from small underpowered studies and resistance patterns differ between geographic regions and over time. When deciding on the optimal empiric therapy for typhoid, antibiotic resistance patterns in the travel destination countries should be considered (3;39). Of particular importance is the increasing prevalence of fluoroquinolone resistance among *Salmonella typhi* isolates from Asia (37).

## Hygiene interventions

Interventions such as hand washing and avoiding high risk foods entail minimal or no risk, inconvenience, or cost, and there is appreciable indirect evidence of benefit in terms of reducing typhoid incidence (38).

## Typhoid vaccine and *Salmonella paratyphi*

Paratyphoid fever, caused by *Salmonella enterica* serovar Paratyphi A, B and C, is a systemic disease with clinical features indistinguishable from typhoid fever. The global burden, estimated at 5.4 million cases annually, may be increasing (6); as is the prevalence of antibiotic resistance and the number of travel-related cases. It is unlikely that injectable Vi vaccines would provide protection because the vaccine elicits antibodies for an antigen that is not present in *S. paratyphi* A and B. In contrast, Ty21a vaccines elicit serum and mucosal antibodies to *S. typhi* O, H and other antigens, which are shared with *S. paratyphi*. However, current evidence is not sufficient to recommend oral typhoid vaccine (Ty21a) for protection against paratyphoid.

## Recommendations and conclusions

The risk of typhoid to travellers is generally low and varies by region. It is highest for travellers to South Asia. The low risk of typhoid combined with the moderate efficacy of the vaccine mean that the benefits of vaccination are modest (efficacy ~50%); however, the vaccines have a good safety profile. Following the review of all evidence and taking into consideration the vaccine efficacy, risk for typhoid and safety profile, CATMAT suggests that the majority of travellers to the South Asia be given typhoid vaccine (Ty21a or Vi polysaccharide vaccine) and not be used for travellers to all other endemic areas (**Table 2**). The recommendations are conditional, due to the moderate confidence in the effect estimate.

**Table 2: Recommendations on the use of typhoid vaccine for Canadian travellers**

Typhoid vaccine	
<b>CATMAT suggests</b>	<ul style="list-style-type: none"> <li>• that typhoid vaccine (Ty21a or Vi polysaccharide vaccine) be used for Canadian travellers visiting South Asia*; <b><i>Conditional recommendation, moderate confidence in estimate of effect.</i></b></li> <li>• that typhoid vaccine (Ty21a or Vi polysaccharide vaccine) not be used for Canadian travellers visiting destinations other than the South Asia; <b><i>Conditional recommendation against immunization, moderate confidence in estimate of effect.</i></b></li> </ul>
* For destinations other than South Asia, typhoid vaccination decisions might be influenced by other factors associated with risk of travel acquired typhoid. Providers should discuss associated risk factors and anticipated vaccination benefits and harms with the traveller.	
“Best practice” or “common sense” recommendations:	
<b>CATMAT suggests</b>	<ul style="list-style-type: none"> <li>• Practitioners should advise travellers to adhere to basic sanitation and food and water precautions.</li> <li>• Providers should discuss with the traveller the anticipated benefits and harms (including financial costs) associated with vaccination, and support the traveller in reaching a decision that is consistent with his/her values and preferences.</li> <li>• While there is evidence that suggests Ty21a protects against paratyphoid, it is not sufficient to recommend this vaccine (as an unlabelled use) for this purpose.</li> <li>• The first line drug of choice to treat typhoid are fluoroquinolones however, local antimicrobial resistance patterns in the country of travel need to be considered when choosing empiric therapy.</li> </ul>

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## Conflict of interest

There are no conflicts of interest to declare.

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## Appendix

Recommendation categories	
<b>Strong* recommendation <u>for</u></b>	The committee believes that all or almost all well informed people would want the recommended course of action and only a small number would not. <u>Implication for practitioners:</u> The balance of risks and benefits are such that most travellers would choose the intervention.
<b>Strong recommendation <u>against</u></b>	The committee believes that all or almost all well informed people would <u>not</u> want the recommended course of action and only a small number would. <u>Implication for practitioners:</u> The balance of risks and benefits are such that most travellers would <u>not</u> choose the intervention.
<b>Conditional** recommendation <u>for</u></b>	The committee believes that the majority of well-informed people would want the recommended course of action, but a minority (perhaps a large minority) would not. <u>Implication for practitioners:</u> With a conditional recommendation different travellers may make different choices. Practitioners should present the risks and benefits of the intervention and help each traveller make a decision consistent with his/her values and preferences.
<b>Conditional recommendation <u>against</u></b>	The committee believes that the majority of well-informed people would <u>not</u> want the recommended course of action, but a minority (perhaps a large minority) would. <u>Implication for practitioners:</u> With a conditional recommendation different travellers may make different choices. Practitioners should present the risks and benefits of the intervention and help each traveller make a decision consistent with his/her values and preferences.

Adapted from the GRADE handbook for grading quality of evidence and strength of recommendations and GRADE guidelines 14 and 15 (40-42).

\*The GRADE working group suggests that if a recommendation is “strong”, then it is expected that 90% or more of informed individuals would choose (or not choose) the recommended course of action.

\*\* The GRADE working group suggests that if a recommendation is “conditional”, then it is expected that less than 90% of informed individuals would choose (or not choose) the recommended course of action.

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

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

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

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

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

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

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

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

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

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

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

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

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