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Microbiological stool testing in adults and children with diarrhea: relevance and measures to promote judicious use

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SUMMARY

Microbiological stool testing in adults and children with diarrhea: relevance and measures to promote judicious use

Introduction

Diarrhea is the distinctive clinical presentation of gastroenteritis. It is often infectious in origin and is self-resolving. However, certain clinical presentations require an investigation to determine the etiology of the diarrhea and to permit adequate management of the person at risk for complications. The investigation consists primarily of microbiological stool testing which can detect bacterial, parasitic or viral enteropathogens responsible for infectious gastroenteritis.

Due to some concerns about requests for microbiological stool tests that are not clinically warranted (particularly those for parasites), the Ministère de la Santé et des Services sociaux (MSSS) asked the Institut national d'excellence en santé et en services sociaux (INESSS) to produce clinical decision support tools to promote judicious use of these laboratory analyses, especially by front-line health professionals. The objective of this work was to make recommendations regarding the situations justifying a request for microbiological stool testing, in order to guide and harmonize the practice across the province. This work and the consultative process involved also led to the development of a set of recommendations aimed at improving the organization and continuum of services.

Methodology

This work was based on a review of the best available scientific data evaluated by the authors of clinical practice guides (CPGs) and clinical guidelines (CGs), supplemented by experiential knowledge gathered from various stakeholders through an informal deliberative process. The systematic search for guides and guidelines was conducted in several bibliographic databases and covered the period from January 2007 to December 2019. A search was also conducted in September 2017 and again in December 2020 by consulting the websites of health technology assessment agencies and organizations, government agencies, and professional associations and bodies associated with the topic of interest. In August 2021, a final verification of these organizations was carried out to check if they had published any new documents that were appropriate for inclusion. Documents were selected according to predefined exclusion and inclusion criteria, and the retained items were assessed for methodological quality using validated tools. These steps were carried out independently by two professional scientists. The relevant information and recommendations were then extracted by one professional scientist and validated by the other. The results were presented in tables and summarized in the form of a narrative synthesis. A professional scientist performed a quantitative synthesis and a budget impact analysis of the costs associated with judicious use of the bacterial and parasitic nucleic acid amplification tests (NAATs) currently listed in the *Répertoire*

québécois et système de mesure des procédures de biologie médicale (the *Répertoire*), for the fiscal years 2018 to 2020. The perspectives of clinicians on current practice and contextual issues, considering the information from the retained publications, were gathered from the advisory committee members representing various specialties and areas of expertise, the external reviewers and the members of both the monitoring committee and the standing scientific committee on laboratory tests. Following knowledge triangulation, preliminary proposals regarding clinical information critical for decision-making and clinical recommendations on situations warranting microbiological stool testing were made and then shared as a first iteration with the advisory committee members. Two additional iterations were required before approval of formulations by a majority of the committee members. During these discussions, the members were also invited to give feedback on the applicability, acceptability and potential impact of the clinical recommendations. Consideration of the contextual issues, particularly the barriers to judicious use of such testing beyond the clinical aspects identified during the consultations, led to formulation of recommendations on implementation, intended for the Ministère de la Santé et des Services sociaux (the ministry), health-care institutions and laboratories. These recommendations were shared with professional orders, federations and associations to gauge their acceptability and applicability in each setting concerned. The recommendations on implementation were developed and discussed with the members of the advisory and monitoring committees.

Results

Based on the information gathered, it appears that the criteria for requesting bacterial or viral stool testing are relatively well understood by clinicians, while those for parasite testing are challenging for some professionals, especially those working on the front lines. The decision-making process leading to requests for microbiological stool analysis has therefore been clarified, with criteria based on duration, severity, specific clinical situations, risk of exposure to enteropathogens, and the possibility that the diarrhea is not of infectious etiology, for both the adult and pediatric populations.

Infectious diarrhea (especially if suspected of being viral) usually requires no investigation. The precautionary principle must nonetheless be applied, unless the affected person presents with rectal bleeding, fever or severe abdominal pain, or an immunodeficiency, especially in the presence of impaired cellular immunity, or when the diarrhea has persisted for at least 7 to 10 days. In such cases, bacterial stool analysis is necessary. In the case of rectal bleeding associated with recent travel to an endemic country, or when diarrhea persists for more than 14 days with no sign of improvement, parasitic stool testing is also warranted. In addition, it is clinically appropriate to order parasite microbiological testing when the results of the bacterial analysis are negative, especially if the diarrhea has lasted for at least 10 to 14 days. Beyond such steps, a microbiology/infectious disease physician, a pediatrician or a gastroenterologist is usually consulted. These test requests require the collection of a single stool specimen to test for bacteria and parasites, unless the parasite of interest is only detectable by microscopy, in which case two or three specimens are needed.

Certain clinical information appears to be essential for guiding the laboratory in the use of appropriate techniques for bacterial, and especially parasitic, testing. In particular, laboratories must be informed of the presence of rectal bleeding or mucus in the stool, of the risk of exposure (travel, immigration or international adoption, contact with farm or sick animals) and of the immune status of the symptomatic person. However, most requisition forms do not permit quick input of this clinical information, and clinicians are not required to include it, which can contribute to inappropriate use of microbiological stool tests. The province's laboratory information system (LIS), whose implementation will start in late 2021, has the potential to improve the input fields for these tests in the data entry software and on the requisition forms. The heterogeneity of the request forms both within and between clusters (that is, groups of medical laboratories) poses a challenge for judicious use of these tests, given the varying and sometimes incomplete clinical information provided to the laboratories, depending on the region of Québec concerned. Harmonizing the microbiological stool test requisition process across the province could therefore facilitate tasks for the requesting physicians and laboratories. Also, incomplete information and errors in transcription and data input by the personnel sending the request electronically to the laboratory can lead to its cancellation by the laboratory, raising an additional issue. Lastly, when the request is processed and the analyses are completed, the laboratories generate a report containing a list of the microorganisms found in the stool, which is sent to the requesting clinician. The patient's condition may then require the involvement of a microbiology/infectious disease physician, pediatrician or gastroenterologist to assess the need to initiate treatment. In such cases, the laboratory report could include information on the pathogenicity or non-pathogenicity of the microorganisms found, especially regarding parasites, to better guide the clinician.

A stepwise approach to investigating suspected infectious diarrhea can have a positive impact on reducing the number of clinically unwarranted analysis requests. Such a diagnostic approach should therefore be encouraged. However, other issues also contribute to requests for microbiological stool tests that are not clinically relevant, thus increasing laboratory workload, slowing down the production of results and consequently delaying the diagnosis of gastroenteritis or another clinical condition. Indeed, most Québec laboratories identify enteropathogens via conventional techniques (e.g., stool culture and microscopy), which results in turnaround times of up to 4 to 5 days for bacteria and several weeks for parasites. Requesting clinicians might thus be inclined to order multiple microbiological stool tests simultaneously to expedite patient management whereas the requests should be processed in order of priority based on the clinical presentation.

The nucleic acid amplification test detects enteropathogens and yields results quickly and with greater sensitivity, reducing result turnaround times, especially for tests for parasites. According to Centralab data, most bacterial testing is done with stool cultures, which generates costs of over $1 million annually, even though they detect only five types of bacteria, whereas, at a similar cost per test unit, NAAT detects seven strains of bacteria as well as Shiga toxins. However, Centralab's supraregional designation limits its implementation to the four clusters that have laboratories in the province's teaching hospitals. For parasite testing, microscopy (for which producing results is laborious and

time-consuming) is the main technique used in Québec and has a lower overall per-unit cost than NAAT. However, NAAT detects the four parasites most commonly found in stool quickly and simultaneously. The use of this parasite test, which has been implemented in six clusters, depends however on the prioritization of needs by the laboratories, since its inclusion in the *Répertoire* does not oblige it to be used. Therefore, the benefit of NAAT being used for enteric bacteria and parasite detection by those laboratories that are not already doing so rests on the fact that it could support clinicians in the judicious use of microbiological stool tests by speeding up result turnaround times. However, it does not replace bacterial culture in notifiable disease (*maladie à declaration obligatoire,* MADO) situations, antibiotic susceptibility testing or parasite analyses, which are not part of the current parasite NAAT kit and analysis 45098 registered in the *Répertoire*.

Based on the assumptions used for the budget impact analysis of the bacterial and parasitic NAATs currently listed in the *Répertoire,* and on the sensitivity analyses performed to assess the impact of varying the weighted value (± 20%) and the number of tests (± 20%), the estimates for the regional deployment of bacterial and parasitic NAATs and the judicious use of these tests could vary from $1.8M in savings to $2M in additional costs. The expected savings would be even greater if the weighted value associated with the tests or the number of tests were lowered.

Conclusion

While not a substitute for clinical judgment, the recommendations made and the decision support tool developed on their basis should promote the judicious use of microbiological stool tests, reduce workload at microbiology laboratories, and improve result turnaround times. The overall emphasis of the proposed recommendations is on clarifying the key elements to be taken into account when making a clinical evaluation, on the choice of microbiological stool tests according to the clinical situation, and on the situations where consulting a microbiology/infectious disease physician, pediatrician or gastroenterologist should be considered. The potential resulting practice changes will depend, however, on the dissemination of the tool, the adherence to these changes, and the uptake of the related recommendations by the health professionals concerned. Monitoring the volume of tests over the next few years should allow assessment of the impact of INESSS's recommendations on the use of microbiological stool tests with regard to the various parameters discussed in this report.

Implementation recommendations

In light of all the findings, INESSS has made a set of clinical, professional and organizational recommendations aimed at improving the quality of care by attempting, in particular, to reduce the workload at microbiology laboratories and the specimen processing and result turnaround times through a more judicious examination of the situations where microbiological stool testing is appropriate.

At the clinical level, regarding the process of decision-making on microbiological stool testing

The recommendations are featured in the decision support tool primarily intended for front-line clinicians. The conditions warranting or not warranting the use of microbiological stool tests are as follows:

CLINICAL RECOMMENDATIONS FOR DECISION-MAKING REGARDING THE USE OF MICROBIOLOGICAL STOOL TESTING ***! These recommendations are not a substitute for clinical judgment.***
Microbiological stool testing not clinically warranted
Diarrhea of less than 7 days in duration (especially if in recent contact with a person with gastroenteritis) and: • overall stable condition of the person (based on clinical judgment); • no bloody stools or fever.
Bacterial stool testing warranted on the basis of the clinical situation
Diarrhea accompanied by at least one of the following clinical conditions: • fever; • bloody stools; • severe abdominal pain and significant dehydration (in the clinician's judgment); • immunodeficiency, especially with impaired cellular immunity; • more than 6 bowel movements in 24 hours accompanied by a deterioration in the person's overall state; • diarrhea lasting at least 7 to 10 days with no sign of improvement; and, based on clinical judgment, dietary exposure also considered via consumption of unpasteurized milk, poorly cooked meat, spoiled food (risk of *Listeria*, vigilance in pregnant women required), raw fish or seafood (risk of *Vibrio* or *Plesiomonas*) or travel to endemic areas (risk of pathogens specific to the country) ; • Diagnostic uncertainty.

Parasitic stool testing warranted on the basis of the clinical situation

Diarrhea accompanied by at least one of the following clinical conditions:

- bloody stools and having returned from travel to or immigration or adoption from an endemic area (risk of *Entamoeba histolytica*);
- diarrhea lasting for more than 14 days with no sign of improvement, depending on the clinical presentation and the clinician's judgment (risk of *Giardia*);
- diarrhea lasting for 10 to 14 days with no sign of improvement with microbiological stool testing negative for bacteria and at least one of the following factors:
  - travel to or immigration or adoption from an endemic country (risk of *Cryptosporidium*, *Entamoeba histolytica*, *Giardia* or country-specific pathogens);
  - child care, health care or laboratory worker or exposure in a prison setting (risk of *Giardia*);
  - preschool-age children or contact with preschoolers (risk of *Giardia*);
  - consumption of surface well, stream, river or lake water (risk of *Giardia* or *Cryptosporidium*);
  - consumption of unsafe food, raw fish or seafood;
  - contact with sick pets or with farm animals;
  - sexual practices involving exposure to fecal microbiota (risk of *Entamoeba histolytica* or *Giardia*);
  - link with a waterborne community diarrhea outbreak (risk of *Cryptosporidium*);
  - immunodeficiency, especially with impaired cellular immunity;
  - diagnostic uncertainty and according to clinical judgment.

At the organizational level

This work also identified areas where health professional knowledge needs be strengthened. Thus, INESSS has made two recommendations for the overall improvement of knowledge and expertise pertaining to microbiological stool tests.

RECOMMENDATIONS REGARDING OVERALL IMPROVEMENT OF KNOWLEDGE AND EXPERTISE PERTAINING TO MICROBIOLOGICAL STOOL TESTING

- The professional orders, federations and associations concerned **should** make their members aware of:
  - the situations where stool testing for bacteria, viruses or parasites is indicated;
  - the importance of documenting crucial clinical information for the laboratory on the test requisition forms;
  - the number of specimens required for microbiological stool testing for bacteria, viruses and parasites.
- Educational institutions, in particular the faculties of medicine and nursing at the various Québec universities, and workplaces and other bodies concerned that provide training, specifically to medical administrative officers and assistants, and to medical file clerks **should** ensure that up-to-date basic training on microbiological stool testing is available to their students or to the personnel concerned.

To improve the diagnostic continuum and promote judicious use of microbiological stool testing, to shorten turnaround times, and to reduce the workload of those laboratories that are still using time-consuming and laborious techniques on a first-line basis, INESSS has made two recommendations for the deployment of NAAT for bacterial and parasitic stool testing in all of the province's cluster laboratories, since it is the fastest and most sensitive molecular method.

RECOMMENDATIONS REGARDING IMPROVEMENT IN THE TESTING PROCESS
The ministry **should** expand the designation of bacterial NAATs, coded as 45043, from supraregional to regional so that they can be implemented province-wide in the laboratories in all the clusters.
The ministry **should strongly encourage** the designated cluster laboratories to implement bacterial multiplex NAAT to test for the *Salmonella*, *Shigella*, Shiga toxin-producing bacteria, *Yersinia enterocolitica*, *Campylobacter*, *Vibrio* spp., and *Aeromonas* spp. enteropathogens, which are listed in the *Répertoire* with the code 45043, and parasitic multiplex NAAT to test for the *Cryptosporidium* sp., *Dientamoeba fragilis*, *Entamoeba histolytica* and *Giardia lamblia* enteropathogens, which are listed in the *Répertoire* with the code 45098. Appropriate support would ensure the successful implementation of NAAT for microbiological stool testing in the designated laboratories. Consideration should be given to preventing the loss of microscopy expertise that could result from this recommendation.

In addition, in order to harmonize practice regarding the number of specimens to be submitted when ordering microbiological stool testing, to reduce the number of cancelled test requests and to limit the performance of unwarranted tests, INESSS has made five recommendations aimed at standardizing the practice at the regional, or even provincial, level, and at improving the transmission of relevant clinical information to laboratories.

RECOMMENDATIONS REGARDING HARMONIZATION OF PRACTICE AND IMPROVING TRANSMISSION OF RELEVANT CLINICAL INFORMATION TO LABORATORIES
The ministry **should strongly encourage** the laboratories in a given cluster to harmonize their instructions regarding the submission of only one sample per 7-day period for microbiological testing for bacteria.
The ministry **should** ensure, in the configuration of the province's laboratory information system (LIS), the creation of input fields dedicated to microbiological stool testing (checkboxes or drop-down menus) to capture crucial clinical information for the laboratories[1].
The microbiology laboratories within a given CLUSTER that offer NAAT **should** develop and standardize the information on test requisition forms, for which there would be dedicated fields for stool testing for **parasites** and mandatory tickable subfields or a drop-down menu if a computerized version were available, for parasite testing to be performed specifically by NAAT or by another technique, if deemed necessary.

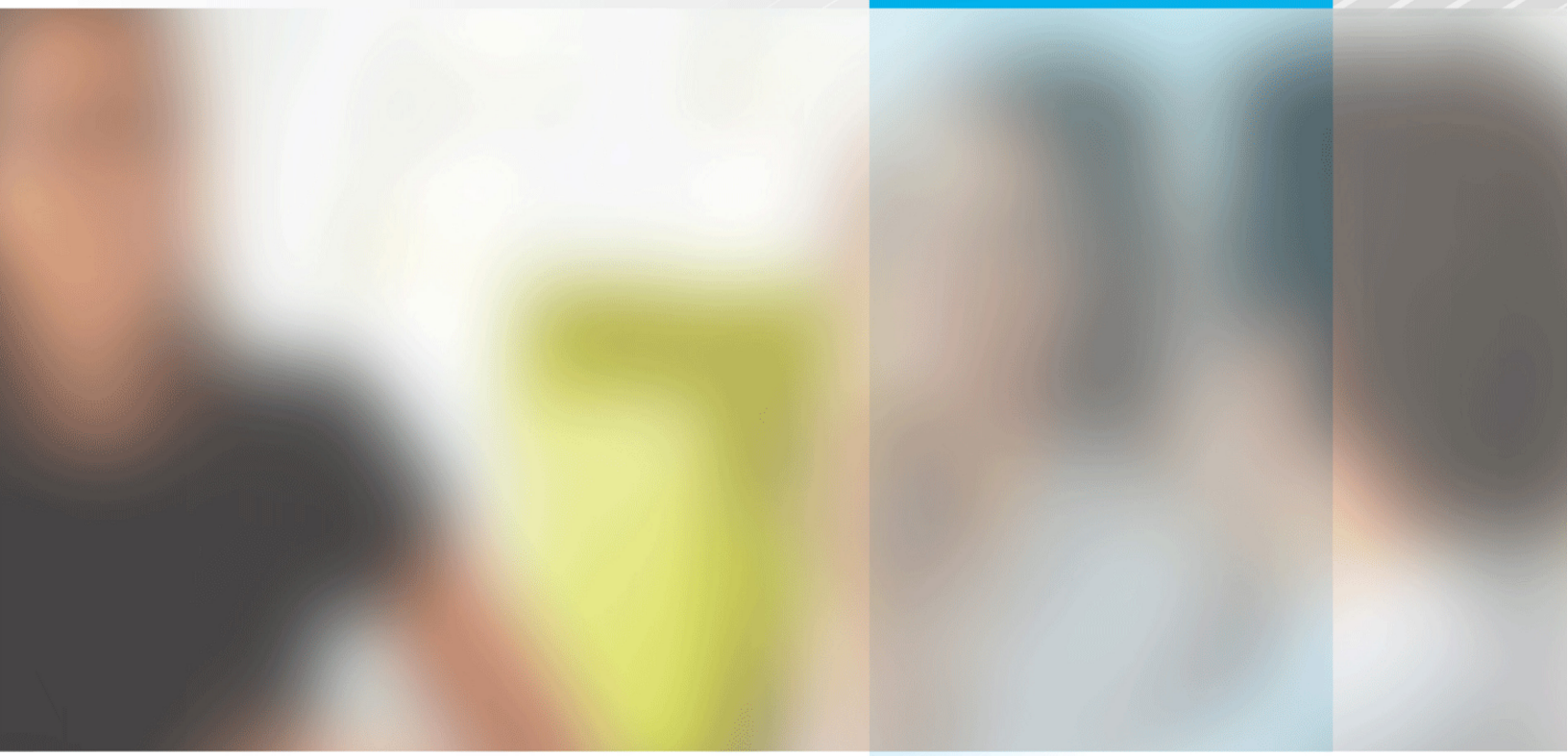
[1] Presence of blood or mucus in the stool, immigration, adoption or return from travel to an endemic country, or contact with sick pets or with farm animals or a person with an immunodeficiency.

RECOMMENDATIONS REGARDING HARMONIZATION OF PRACTICE AND IMPROVING TRANSMISSION OF RELEVANT CLINICAL INFORMATION TO LABORATORIES
The microbiology laboratories within a given CLUSTER **should** develop and standardize the information on test requisition forms, for which there would be dedicated fields for microbiological stool testing and, if checkboxes or a drop-down menu were not available, a space for the requester to enter crucial clinical information for the laboratories[2]. *Absence of this information should not be a reason for laboratories not to perform the analyses. The clinician must be informed that, without the relevant clinical information, the results will have to be interpreted with this proviso or that the test could be refused in some cases.*
Health care institutions and facilities **should** sensitize personnel who enter details into the laboratory information system to the importance of recording the information provided on the requisition form by the clinician or by the user, if applicable.

Lastly, in order to reduce the number of questions from requesting clinicians about microbiological stool test results, INESSS has made a recommendation that information be added to the laboratory test reports transmitted to requesters.

RECOMMENDATION REGARDING THE TRANSMISSION OF TEST RESULTS TO REQUESTERS
The ministry **should** include, via the province's laboratory information system, a field on the microbiological analysis report transmitted to the requester which indicates the pathogenicity or non-pathogenicity of detected parasites.

[2] Presence of blood or mucus in the stool, immigration, adoption or return from travel to an endemic country, or contact with sick pets or with farm animals or a person with an immunodeficiency.



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