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A hospital-level cost-effectiveness analysis model for toxigenic *Clostridium difficile* detection algorithms

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SUMMARY

Background: Despite thorough analyses of the analytical performance of *Clostridium difficile* tests and test algorithms, the financial impact at hospital level has not been well described. Such a model should take institution-specific variables into account, such as incidence, request behaviour and infection control policies.

Aim: To calculate the total hospital costs of different test algorithms, accounting for days on which infected patients with toxigenic strains were not isolated and therefore posed an infectious risk for new/secondary nosocomial infections.

Methods: A mathematical algorithm was developed to gather the above parameters using data from seven Flemish hospital laboratories (Bilulu Microbiology Study Group) (number of tests, local prevalence and hospital hygiene measures). Measures of sensitivity and specificity for the evaluated tests were taken from the literature. List prices and costs of assays were provided by the manufacturer or the institutions. The calculated cost included reagent costs, personnel costs and the financial burden following due and undue isolations and antibiotic therapies. Five different test algorithms were compared.

Findings and conclusion: A dynamic calculation model was constructed to evaluate the cost:benefit ratio of each algorithm for a set of institution- and time-dependent inputted variables (prevalence, cost fluctuations and test performances), making it possible to choose the most advantageous algorithm for its setting. A two-step test algorithm with concomitant glutamate dehydrogenase and toxin testing, followed by a rapid molecular assay was found to be the most cost-effective algorithm. This enabled resolution of almost all cases on the day of arrival, minimizing the number of unnecessary or missing isolations.

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Introduction

Clostridium difficile is responsible for approximately 25% of antibiotic-associated diarrhoea and more than 95% of pseudomembranous colitis.[1,2] Furthermore, this anaerobic bacterium is a major cause of nosocomial diarrhoea in hospitalized patients.[3] Due to its increasing prevalence, the escalating severity of infection and the nosocomial dissemination of *C. difficile*, there is growing interest in rapid and efficient screening tools.

The diagnostic performance of different algorithms for the detection of toxigenic *C. difficile* strains in hospitalized patients has been compared in several studies.[4–14] Barbut *et al.* evaluated the use of simultaneous detection of toxins and glutamate dehydrogenase (GDH).[3] Planche *et al.* compared the analytical performance of commercial toxin enzyme immuno-

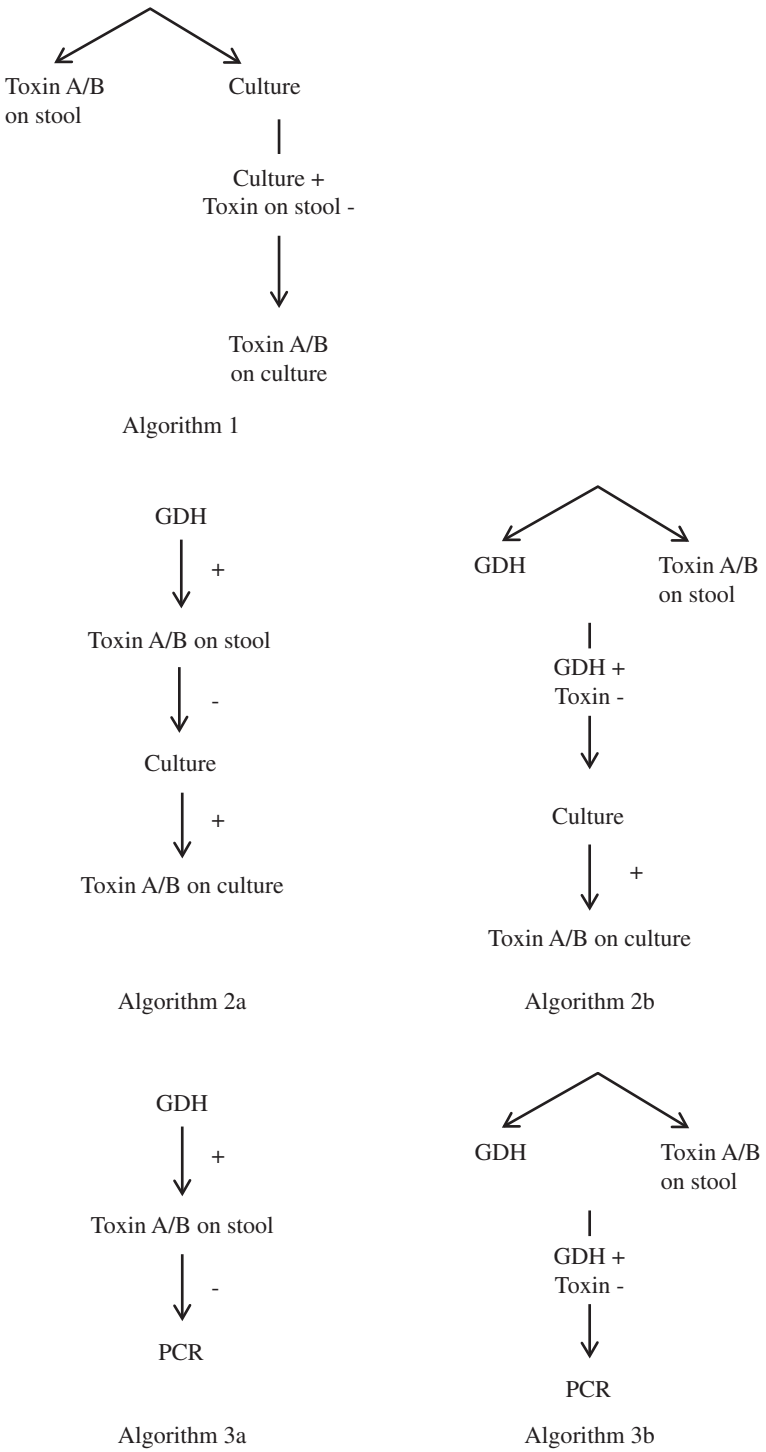

Figure 1. Overview of the tested algorithms. PCR, polymerase chain reaction; GDH, glutamate dehydrogenase.

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assay (EIA) tests with toxigenic culture and cytotoxicity assays.[14] In other studies, the use of two- or three-line testing has been evaluated.[4–6,13] Overall, GDH has high sensitivity (up to 100% in some studies) compared with toxin assays, which are characterized by higher specificity. Bearing the prevalence of *C. difficile* in mind, these results justify a multi-stage testing approach, and several different test algorithms and different flows are in current use.

Financial constraints may motivate hospitals to rationalize their expenses in a consolidated healthcare environment. However, despite thorough analysis of test performance at laboratory level, only a limited number of studies[15] have clearly evaluated the cost impact at hospital level, considering institution-specific variables including request behaviour and infection control policy in case of a positive screening for *C. difficile* infection (CDI). Therefore, the aim of this work was to compare the total cost effectiveness of different toxigenic *C. difficile* screening algorithms and tests used in Flemish hospitals, differentiated by local prevalence and hospital policies for isolation, therapy and disinfection.

Methods

The working strategy for the detection of toxigenic *C. difficile* in seven Flemish hospital laboratories (total approximately 5000 beds) was analysed, and three detection algorithms were selected (Figure 1). Only stools taking the shape of their container were sent to the laboratory for *C. difficile* investigation. Three different toxin assays were selected for comparison: (1) Immunocard tox AB (Meridian Bioscience Inc., Cincinnati, OH, USA); (2) Vidas Tox CD A/B (bioMérieux SA, Marcy L'Etoile, France); and (3) Quik Chek A/B (Techlab, Blacksburg, VA, USA). Three different GDH assays were also selected for comparison: (1) Immunocard GDH (Meridian Bioscience Inc); (2) Quik Chek Complete GDH (Alere, Waltham, MA, USA); and (3) Quik Chek GDH (Alere). The analytical performance (sensitivity and specificity compared with toxigenic culture) of the commercial tests was taken from the literature as weighed calculations. The test specifications are summarized in Table I.

In the first algorithm (Algorithm 1), a toxin assay and culture were performed on *C. difficile* agar (bioMérieux) (according to local procedures) on all samples on the day of arrival (Day 0). Toxin-positive cases were reported for isolation and therapy. On Days 1–3, culture media were examined for growth, and suspicious colonies were tested for toxins with a commercially available EIA test. In the second algorithm, both GDH and toxin tests were performed: either a GDH test was performed first on all samples followed by EIA toxin testing on the GDH-positive samples alone (Algorithm 2a), or both tests were performed concomitantly on all samples (Algorithm 2b). In this algorithm, GDH- and toxin-positive cases were isolated and treated from Day 0. GDH-positive and toxin-negative cases were further tested with toxigenic culture. Algorithm 3 was similar to Algorithm 2, but with a rapid molecular assay replacing the toxigenic culture, resulting in a definitive answer for virtually all samples on Day 0 (Algorithms 3a and 3b). For all these algorithms, the various toxin EIA or GDH assays can be interchanged.

In order to compare the total cost over a one-year period (2010) of the different test algorithms using different commercial assays in different hospital settings (e.g. prevalence, request behaviour, etc.), a two-part calculating model was constructed. The first part considered the cost of the assays performed and the personnel cost. The second part covered the linked hospital costs (e.g. isolation and therapy).

Table I
Details of the available assays including analytical performances, principle, price and time for completion

Test (manufacturer)	Principle	Sensitivity	Specificity	List price(€) VAT excl.	Hands-on time (min)	NPV	PPV	References
GeneXpert (Cepheid, Synnyvale, CA, USA)	PCR	0.96	0.97	35	5	0.995	0.797	4,5
Immunocard A (Meridian Bioscience Inc., Cincinnati, OH, USA)	Membrane-type EIA	0.62	0.99	5.67	5	0.996	0.953	7,8
Immunocard GDH (Meridian Bioscience Inc., Cincinnati, OH, USA)	Membrane-type EIA	0.89	0.95	5.55	3	0.965	0.624	6
Immunocard tox AB (Meridian Bioscience Inc., Cincinnati, OH, USA)	Membrane-type EIA	0.54	0.99	9	5	0.947	0.910	9,12
Quik Chek A/B (Inverness Techlab, Blacksburg, VA, USA)	Membrane-type EIA	0.54	0.99	7.75	5	0.947	0.818	11,12
Quik Chek Complete GDH (Inverness Techlab, Blacksburg, VA, USA)	Membrane-type EIA	0.96	0.93	4.875	3	0.994	0.605	4,13
Quik Chek Complete Tox (Inverness Techlab, Blacksburg, VA, USA)	Membrane-type EIA	0.57	1	4.875	5	0.951	0.956	4,13
Quik Chek GDH (Inverness Techlab, Blacksburg, VA, USA)	Membrane-type EIA	0.96	0.93	7.75	3	0.993	0.594	6,11
Vidas Tox CD A/B (bioMérieux SA, Marcy l'Etoile France)	Automated immuno-assay	0.44	1	5.8	5	0.937	1	4

NPV, negative predictive value; PPV, positive predictive value; PCR, polymerase chain reaction; EIA, enzyme immuno-assay.

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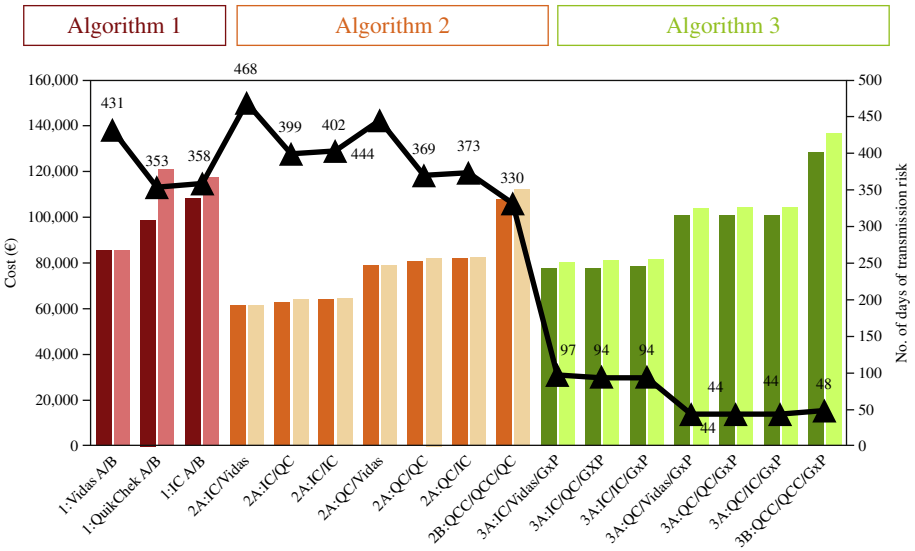

Figure 2. Total cost of the tested algorithms including the number of days of transmission risk. For each test/algorithm, the first bar represents the sum of the cost of the reagents and personnel, and the second (lighter) bar represents the cost of the reagents, personnel and unnecessary isolation days. The dark line shows the number of days of transmission risk for each algorithm. GxP, GeneXpert; IC GDH, ImmunoCard GDH; IC AB, ImmunoCard toxinA/B; QC GDH, QuikChek GDH; QC AB, QuikChek toxin A/B; QCC AB, QuikChek Complete toxin A/B; QCC GDH, QuikChek Complete GDH.

Additionally, the number of days for which patients infected with toxigenic strains were not isolated, and therefore constituted a risk for secondary nosocomial infections (days of transmission risk), was calculated. For each assay in the algorithm, the prevalence of CDI in the individual institutions was used to calculate the number of tests.

The total cost of the testing was calculated using the following formula:

$$\sum_{test=1}^{n} [(N \times price\ of\ test\ n) + (N \times minutes\ to\ perform\ test\ n \times analyst\ labour\ cost\ per\ minute)]$$

where n is the different tests and N is the number of samples for the specific tests, calculated with respect to prevalence and test performances as mentioned above.

List prices for the different tests were provided by the manufacturers (Table I). A fixed technician cost of €0.65/min was used, based on real labour cost in the aforementioned institutions.

For all hospitals, a positive screening on Day 0 or a positive confirmation test on Days 1–3 prompted patient isolation and antibiotic therapy for a minimum of three days (until resolution, defined as 24 h without diarrhoea), to be recalled in case of a negative confirmation assay. The minimum attributable cost of one day of isolation and antibiotic therapy was €100 and €13.8, respectively. Based on data from the literature, a minimum cost of €4000 should be allocated to each new nosocomial CDI.[16–24] The hospital cost was calculated as two days of isolation and therapy for each unnecessary isolation day for the specific completed test algorithm. A cost calculation model was built in Excel 2010 (Microsoft Corporation, Redmond, WA, USA) using the aforementioned calculations. The model with the different algorithms is available on http://www.bilulu.be/index.php/activities/project-request/projects-running, including instructions for use (in English).

Results

In the group of selected hospitals, 173,945 patients were hospitalized during the study period (2010). *C. difficile* investigation was requested for 4952 patients (2.8%; range 1.9–4.5%). In total, 308 (0.18%; range 0.1–0.26%) admitted patients tested positive, which accounted for 6.2% (range 3.2–10.7%) of all tested patients. For each tested patient, an average of 1.4 (range 1.2–1.8) samples were sent for *C. difficile* testing. Of the tested samples, 5.5% (range 3.0–10.8%) were positive.

The analysis of the working strategy for the detection of toxigenic *C. difficile* resulted in three general types of test algorithms (Figure 1). The negative and positive predictive values compared with toxigenic culture of the tests included in this study are shown in Table I. These data indicate the false-negative and false-positive outcomes of each test, which have an important implication on calculation of the number of days of transmission risk as well as on the financial impact.

Figure 2 shows the financial impact of the different algorithms, taking into account the different tests, labour costs and unnecessary isolation days. The cost of Algorithm 1 ranged from €85,237 to €120,850. This algorithm also resulted in a high number of days of transmission risk (range 353–431 days). The cost of Algorithm 2a was estimated to range between €61,577 and €82,477, which is lower than that for Algorithm 2b (€112,227). Although the tests used in this algorithm were cheaper, the number of days of transmission risk remained high (range 330–468 days). The cost of Algorithm 3 ranged between €80,037 and €136,384. The number of days of transmission risk was significantly lower for this algorithm (range 44–97 days).

Discussion

The number of detected cases differs with respect to local prevalence and request behaviour, determining the pre-test

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probability, and results in differences in negative and positive predictive values of the assays. Furthermore, different cost fluctuations (reagents, labour) and changes are associated with the available assays, each with their specific test performances. These variables have a direct impact on the cost effectiveness of a given algorithm and assay choice. Therefore, a dynamic model was developed as a counting tool in which these variables can be interchanged.

The model was used to analyse the current testing strategies and assays in seven Flemish hospitals. Algorithm 1 was the most expensive. Indeed, in this scenario, two tests, of which one is a labour-intensive culture technique, were performed on all samples. Additionally, the poor sensitivity of the toxin assays resulted in a large number of false-negative cases on Day 0. As a consequence, the number of days of transmission risk was very high in this algorithm. Algorithm 2 (particularly 2a) was less expensive. Due to the low general prevalence of CDI in the study population, more than 90% of all samples, requiring only one screening test (GDH), could be reported on Day 0. On the other hand, as Algorithm 2a uses successive use of the two tests, sensitivity was lower, resulting in a minor increase in the number of false-negative results. Due to the concomitant execution of the two assays on all samples in Algorithm 2b, the cost was higher. Overall, Algorithm 2 obtained a similar number of days of transmission risk as Algorithm 1.

Algorithm 3 resulted in a significantly lower number of days of transmission risk because virtually all results were available on Day 0. Algorithm 3a was preferred in the authors' setting as it combines a relatively low cost with a significantly lower number of false-negative cases on Day 1, resulting in a lower burden at hospital level due to the lower risk of additional nosocomial infections. As the cost of each new nosocomial CDI is estimated to be more than €4000, the higher laboratory cost of molecular testing could be compensated by the decrease in the number of hospital days with transmission risk.[25–27]

This study compared the approach of different hospitals towards CDI, considering the cost of sample analysis, patient isolation and secondary infections. This model allows an objective comparison based on clear and standardized criteria. Its dynamic nature with a flexible input of a standard set of variables avoids the possible shortcomings of a classic calculation model. This model anticipates fluctuations in test prices, and allows incorporation of new test kits with other performance qualities. Furthermore, the model attempts to provide a well-documented indication of the hospital-wide cost effectiveness of a particular laboratory testing strategy. Recently, Schroeder *et al*. described a sophisticated study on the same topic.[15] Although the present model was much simpler, the authors were able to confirm the main conclusions of Schroeder *et al*.'s study. Furthermore, to the authors' knowledge, this is the first study on this topic providing a free and user-friendly spreadsheet allowing other institutions to make calculations on the most cost-effective strategy in their specific situation. The model is currently available on www.bilulu.be/index.php/activities/project-request/projects-running and can be used free of charge.

Conclusion

A dynamic counting model with possible input of a set of variables, including local prevalence, test choices and market fluctuations, enables the user to make a cost-effectiveness analysis in different settings, with infection control and therapy costs taken into account.

In the authors' setting, a two-step test algorithm with a successive GDH and toxin test, followed by a rapid molecular assay was able to confirm almost all cases on the day of arrival. The algorithm resulted in no significant risk of unnecessary isolations or missed isolations, and was the most cost-effective system from a hospital-wide point of view.

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Conflict of interest statement
None declared.

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