Market place survey of diagnostic platforms suitable for field hospital or field-use settings

Analysis of suitability for the detection of pre-symptomatic infection-related biomarkers

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IMPORTANT INFORMATIVE STATEMENTS

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Abstract

Defence Research and Development Canada – Suffield Research Centre (DRDC – Suffield Research Centre) has a project examining the suitability of using host-specific factors (biomarkers) as an indication of infection, prior to symptom development in an exposed individual. Should suitable biomarkers be identified following rigorous examination to ensure that they are specific to infection and sensitive enough to be useful, assays for these biomarkers will need to be transitioned from the research laboratory to the Canadian Armed Forces (CAF). Diagnosis of infection with a pathogen, prior to symptom development, could aid the CAF in screening individuals or groups that need to be treated, isolated, or returned to normal duties. During deployment, diagnosis of CAF members exposed or suspected of being exposed to serious pathogenic agents would be done by medical staff in a field hospital or at a forward operating base (FOB), or in the field by the operators themselves in order to identify at-risk individuals or at-risk populations. In order for any diagnostic (Dx) test to be useful under these conditions, the Dx equipment must, at minimum, have a relatively small footprint; have limited consumables and power requirements; and be relatively easy to operate, with minimal maintenance and minimal operator training burden. In order to identify Dx platforms that could meet these requirements, DRDC – Suffield Research Centre initiated a contract to survey Dx platform vendors, and identify Dx platforms that could potentially meet these requirements. This report outlines the key findings from the contract report as it pertains to identifying Dx platforms that could be suitable for detection of biomarkers in a field hospital / FOB setting and hand-held platforms that could be used by operators in the field; a critical evaluation of the contractor's findings by DRDC – Suffield Research Centre subject matter experts (SMEs); and a plan to exploit the findings identified in this report.

Significance to defence and security

Current and next-generation commercial off-the-shelf Dx platforms have the potential to be used or adapted for use in detecting and identifying pre-symptomatic biomarkers of infectious disease in field hospital or field-use settings, thereby offering the CAF the potential to use operator-friendly equipment in a deployed, field-forward setting for early exposure diagnostics.

Résumé

Le Centre de recherches de Suffield de Recherche et développement pour la défense Canada (RDDC – Centre de recherches de Suffield) mène un projet qui porte sur la pertinence d'utiliser des facteurs propres à un hôte (biomarqueurs) comme indicateur d'infection, avant l'apparition des symptômes, chez un sujet exposé. Si un examen rigoureux permet de définir les biomarqueurs pertinents propres à une infection et suffisamment sensibles pour être utiles, il faudra transférer les analyses de ces biomarqueurs du laboratoire de recherche aux Forces armées canadiennes (FAC). Un diagnostic d'infection par un agent pathogène, avant l'apparition des symptômes, pourrait aider les FAC à déterminer s'il faut traiter ou isoler une personne ou un groupe de personnes, ou bien si on peut permettre la reprise des fonctions habituelles. Au cours des déploiements, le diagnostic des membres des FAC qui ont été exposés à un agent pathogène dangereux, ou qu'on soupçonne de l'avoir été, serait établi par le personnel médical dans un hôpital de campagne ou sur une base d'opérations avancée (BOA), ou encore par les utilisateurs eux-mêmes sur le terrain. Cela permettrait de déterminer les personnes ou les populations à risque. Pour qu'un test de diagnostic soit utile dans de telles conditions, l'équipement de test doit, à tout le moins, être relativement peu encombrant, exiger peu de produits consomptibles et d'électricité, et être relativement facile à utiliser, sans nécessiter trop d'entretien ni de formation pour les utilisateurs. RDDC – Centre de recherches de Suffield a attribué un contrat afin de sonder les fournisseurs de plateformes diagnostiques pour déterminer lesquelles pourraient satisfaire à ces exigences. Le présent rapport donne un aperçu des principales conclusions tirées du rapport de contrat en ce qui a trait à la recherche de plateformes diagnostiques pouvant servir à la détection des biomarqueurs dans un hôpital de campagne ou une BOA et de plateformes portatives pour les utilisateurs sur le terrain une évaluation critique des conclusions de l'entrepreneur par des experts en la matière de RDDC – Centre de recherches de Suffield. Un plan visant à tirer profit des conclusions présentées figure également dans le rapport.

Importance pour la défense et la sécurité

Les plateformes diagnostiques commerciales actuelles et de la prochaine génération peuvent être utilisées ou adaptées à des fins de détection et d'identification, dans un hôpital de campagne ou sur le terrain, des biomarqueurs présymptomatiques indiquant la présence d'une maladie infectieuse, permettant ainsi aux FAC d'utiliser un équipement convivial en situation de déploiement sur le terrain, en zone avancée, pour diagnostiquer une exposition précoce.

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1 Introduction

The CAF need to operate and achieve mission success in a Chemical Biological Radiological Nuclear environment thus monitoring of personnel in theatre is critical for identification of individuals that have been potentially exposed to a biological threat (BT) agent, an agent endemic to the area of deployment, or an emerging infectious disease agent, the latter being especially problematic to diagnose as testing may not be available.

Personnel can be infected by a pathogen but disease does not always ensue. For disease to occur, the pathogen must enter the individual (host) in sufficient numbers; by an appropriate route (e.g., inhalation for influenza virus, ingestion for the cholera bacillus); invade and multiply within the appropriate target cells/tissues; and evade the host's immune system. Disease is preceded by an asymptomatic incubation period during which time the agent localizes to the appropriate cells/tissue and starts to multiply within those cells/tissues, followed by a period of non-specific symptoms, such as fatigue, headache, fever, etc., which can also be present in situations other than infectious disease (e.g., tissue injury).

An example of the stages involved in the progression of disease for three BT agents, *Bacillus anthracis* (anthrax), *Francisella tularensis* (tularemia) and Venezuelan equine encephalitis virus (encephalitis) is presented in Figure 1 (adapted from [1]) and includes the pre-symptomatic stage (yellow), the non-specific symptom (flu-like) stage (blue), the disease-specific symptom stage (pink), the time frame in which death usually occurs if treatment is delayed until disease specific symptoms are present (x's), the convalescent stage in which the host's immune system clears the infection (light green), and the period in which sequelae (chronic symptoms) develop (dark green).

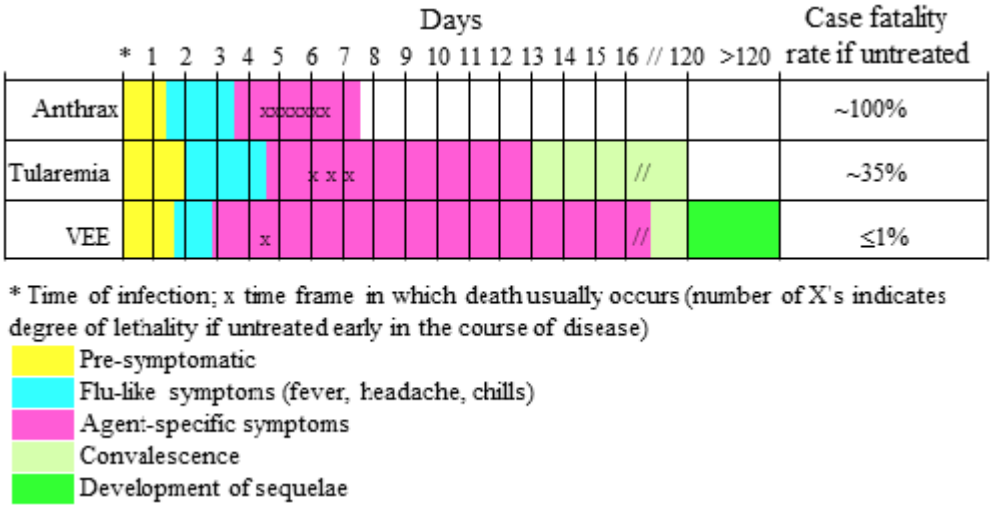

Figure 1: *Course of infection for three biological threat agents.*

During the incubation period, even though the individual is asymptomatic, the infectious agent is replicating within the host and the host is responding to the presence of the infectious agent. This early response by the host is known as the "innate immune" response and is the first line of

defense against a variety of challenges, initiating a cascade of signaling events within the body, eventually resulting in generalized inflammation and development of non-specific symptoms such as fatigue, headache, fever, etc. [2].

DRDC – Suffield Research Centre is examining this early host defense response to identify components that are present prior to symptom development, and prior to the presence of detectable levels of agent using standard methodologies, to see if components of this response could be useful as surrogate markers of infection. A surrogate marker, also known as a biomarker, is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention [3], and should be specific for the disease in question and detectable by a Dx assay that assists in diagnosis, initiation of treatment, and in tracking the progress of the disease [4, 5].

Preliminary studies at DRDC – Suffield Research Centre have identified a number of potential biomarker candidates that are present prior to symptom development. Following vetting of these surrogate markers of infection to ensure that they are sensitive and specific enough to be useful, assays for these markers will have to be transitioned from platforms that are used in the research laboratory to platforms that meet the needs of the CAF.

Consequently, DRDC – Suffield Research Centre initiated a contract to survey Dx technologies and platforms currently available, with a focus on platforms and technologies that would be suitable for use in a field hospital / FOB or by operators in the field (hand-held devices). The contract report summarizing the survey results was previously published [6]. A critical evaluation of the results of the contract report is outlined in this report.

2 Considerations for diagnostic systems for detection of infection-related biomarkers

A Dx system encompasses both the assay and the platform that the assay is performed on. A Dx system must meet a number of important criteria in order to be beneficial to the CAF, since operators may not have extensive laboratory experience and they may be operating under conditions where laboratory resources may be limited. The system must be sensitive and specific enough to detect Dx biomarkers with good predictive value but require minimal sample processing, minimal power requirements, a low operator training burden, and ideally, provide unambiguous interpretation. Some of the more important considerations are outlined below.

2.1 Types of samples

The Dx platform should ideally be able to process multiple specimen types including, but not limited to, blood, serum, urine, saliva and swab samples, all of which are commonly used as Dx samples. Urine, saliva and swab samples are desirable sample types as sample collection does not involve invasive means, but these sample types are not always applicable to the condition being tested for.

2.2 Processing of samples

Sample processing is critical in performance of Dx assays, ranging from minimal processing steps (e.g., hand-held assays (HHAs) used by the CAF) to extensive processing steps (e.g., microarray assays used in a research laboratory). Many assays targeting nucleic acid (NA) require isolation of NA prior to the assay being performed, and require a high level of operator skill and knowledge to perform the assay and interpret the results. Some commercial platforms have begun to integrate sample preparation, analysis, and reporting functions into a single device which reduces the requirement for advanced levels of operator training, e.g., the GeneXpert and the FilmArray, both of which have been, or are being evaluated at DRDC – Suffield Research Centre for the CAF [7, 8].

Assays targeting protein typically require less sample processing than those that target NA, however some assays require multiple manipulations, e.g., enzyme-linked immunosorbent assay, and enzymatic assays that require the reaction to be started and stopped at specific time intervals.

In field hospitals / FOB, some sample processing is tolerable as operator skill level is higher and logistical burden is lower; however, for HHAs performed in the field, pre-processing requirements should be minimal, if at all. Platforms that have integrated sample processing are advantageous in field hospitals / FOBs, as they reduce the logistical burden on the operators, minimize cross-contamination of samples and decrease potential exposure of the operator to infectious agents.

2.3 Number of tests per sample

Dx platforms that are capable of running multiple assays on a single sample (multiplex capability) at the same time are strong candidates because studies have indicated that the determination of whether an individual is infected prior to symptom development will require running tests against multiple different biomarkers at the same time. For example, a four-gene classifier (the SeptiCyte Lab) was evaluated in Australia and the Netherlands [5] for discriminating sepsis from infection-negative systemic inflammation in critically ill patients. Testing demonstrated that the "SeptiScore" value generated by the testing system was able to discriminate patients with sepsis from patients with infection-negative systemic inflammation early after the onset of symptoms [5]. Other studies have reported that biomarker panels consisting of between four and 50 different biomarkers could discriminate individuals with a particular condition [9–14], thus multiplex capability is essential for any system that is to be used for identification of individuals using surrogate markers of infection.

2.4 Types of assays

Biomarkers can be nucleic acids, proteins, or metabolites, and as such require different chemistries (assays) for detection and analysis. A Dx platform often exploits a single detection chemistry for analysis, for example, antibody-antigen (Ab-Ag) reactions for the detection of proteins or polymerase chain reaction (PCR) to detect NA. This can limit the scope of a Dx test; however, technological advances are allowing the consolidation of immunoassay and NA testing into the same device.

Assays for detecting NA typically utilize NA amplification or NA hybridization techniques. NA amplification techniques such as PCR are very sensitive, thus extra care must be taken to maintain clean work areas in order to prevent false positive results arising from cross-contamination. Currently, hand-held Dx systems tend to avoid including PCR chemistry because of the additional time required for the reaction and the additional size/power requirements that may be needed for operation. NA hybridization techniques rely on the base pairing of a single-strand of deoxyribonucleic acid (DNA) with its complementary counterpart. As the NA is not amplified, hybridization technologies tend to be less sensitive than amplification technologies; however, they can be very specific since even a single base change can be detected.

Assays for protein detection have been in use longer than assays for NAs; they have improved over time with respect to increased sensitivity, lower sample volume requirements and faster time-to-result. Protein assays typically detect components of the protein structure (e.g., Ab-Ag, dye-binding or oxidation-reduction reactions) or protein function (e.g., enzymatic reactions). Immunological (Ab-Ag) assays are very common, and have a wide range of sensitivities. Immunological assays performed "in situ", such as HHAs used by the CAF, are not very sensitive, are subject to false positive and false negative results, but they have the advantage that they are very easy to perform, require minimal training and can give immediate information to the operator. Immunoassay sensitivity and specificity can be increased by performing assays "in solution", and by using indirect and capture-based assays.

2.5 Assay detection methods

Detection methods include optical methods which give a "colour" change either in the visible or ultraviolet spectrums, and non-optical systems such as electrochemical (EC) or radiological methods. Each detection method has its own advantages and disadvantages, and differs with respect to detection sensitivity. Some are more appropriate for use in a research lab than for use in the field.

Assays for detecting NA and proteins primarily utilize optical detection systems. Optical systems are commonly used in field hospitals / FOB, or more advanced laboratories, and less so for hand-held/field-use, due to requirements for alignment of the optical system, larger size, and increased power requirements, although improvements in optical detection technology are reducing some of these barriers.

EC detectors utilize biosensors in an analytical device that can yield a digital electronic signal proportional to the concentration of a specific analyte or group of analytes [15, 16]. Biosensors (Figure 2) are composed of two elements: a biological recognition element able to interact specifically with an analyte, and a transduction element or transducer able to convert a change in the property of a solution or surface into a recordable signal [17]. The biological recognition element can be an Ab, enzyme, or NA probe. Binding of the analyte to the biological recognition element may generate changes in heat, electrical potential, electron movement, light, or mass which are measured by the appropriate transducer. This change is converted to an electrical signal that is amplified, processed, and displayed as either a quantitative result (e.g., a value) or a qualitative result (e.g., presence/absence).

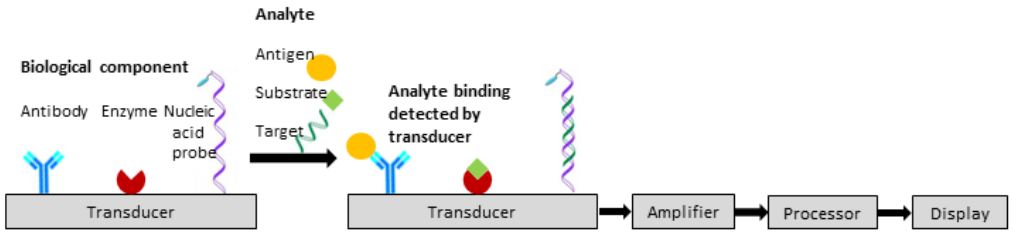

Figure 2: *Schematic diagram of a biosensor.*

Radiological Dx systems are particularly problematic for the CAF during operations as these systems require a pipeline for receipt of the radioactive assay components and disposal of radioactive waste material is a significant concern.

2.6 Features of Dx systems for militarily-relevant settings

The suitability of a Dx platform for a given setting is largely dictated by the desired concept of use. If a Dx platform is used in a research laboratory, it can be larger, it can require consumables that must be stored at refrigerator or freezer temperatures, it can utilize additional pieces of equipment, it can be maintained regularly, and it can be operated by staff that have greater skill and knowledge. Dx systems that are to be used in a field hospital / FOB or are to be used as hand-held systems in the field have significantly different requirements than systems used in a research laboratory. Some of the features of Dx systems to be used in two militarily-relevant settings are outlined below.

2.6.1 Field hospital / FOB setting

A Dx system to be used in a field hospital / FOB should be able to handle a variety of biological sample types; have assays that target a number of different markers; have a short sample-to-answer turnaround time; should be semi-automated or integrated into a system that is capable of higher sample throughput; may require use of additional laboratory equipment; should be portable (although portability is not as much of an issue for field hospitals as it is for use in the field); and should be able to be operated for longer periods of time than equipment used in the field. Thus, throughput and maintenance/lifespan are considered more important for field hospital use than for systems to be used in the field.

During the evaluation of detection equipment for use in a field hospital / FOB setting, sensitivity, mobility, physical system requirements, operational conditions and versatility of sample input were considered as the most important criteria.

2.6.2 Hand-held/field-use setting

A hand-held Dx system to be used in the field is one that would be used by forces or other first responders, typically outdoors in a variety of environments (e.g., arctic, desert, rural, or urban habitats), where these systems could be exposed to more extreme conditions (e.g., heat, cold, humidity) than experienced in a field hospital / FOB. Consequently, these systems need to be small, lightweight, easy to carry, simple to operate with minimal hands-on time, standalone, robust; and have limited electrical requirements, low signature profiles, and disposable/single use tests. Signature minimization is important in the operation of these devices to avoid jeopardizing troop presence and location during operations. Devices that can dim screens or light sources, mute sounds and alarms, and have minimal thermal output are preferred. Thus, signature and operational conditions were considered more important for field-use than for use in a field hospital setting during the evaluation process.

During the evaluation of detection equipment for field-use, factors pertaining to mobility (size and weight), physical system requirements (e.g., battery power, water use), and operational considerations were considered as the most important criteria.

3 Contractor market place survey of diagnostic platform technologies

3.1 Survey methodology

The contractor was tasked with conducting a comprehensive survey of currently available and emerging Dx platforms capable of detecting host-specific biomarkers, to critically evaluate each detection platform/system and to identify top candidate detection platforms suitable for field hospital / FOB and hand-held/field-use [6].

The survey was conducted by the contractor without bias, meaning that DRDC – Suffield Research Centre did not specify preferred assay or detection methods. This was intentional in order to identify as many Dx platforms as possible, including Dx platforms in early stages of development that could have future applications for the pre-symptomatic Dx biomarker project. As already indicated, greater latitude in assay and detection methods could be given to field hospital / FOB use than to field-use because the former is less subject to adverse conditions (temperature of operation, movement during operation, limitations in power supply), size/weight restrictions, and end-users typically have more specialized skill sets.

Vendors for Dx platforms/systems were identified through an examination of peer-reviewed literature, conference proceedings, exhibitor lists from national and international scientific meetings, reports on similar topics, as well as searches of granting agencies and scientific partnership webpages.

The contractor prepared and sent a survey to 215 vendors which addressed parameters such as:

- Vendor contact information including company name, platform model number, address, contact person, web address and cost of platform;
- Molecular Dx platform details including type of biomarker detected, type of detection chemistry, open or closed system, single or multiplexed assays, clinical sample requirements, sample throughput, level of automation, sample processing time, analysis at point-of-care and cost per test;
- Platform/instrument parameters including size, weight, portability, utility requirements (power, water, gas), signature, availability of battery power, operating environmental conditions, maintenance requirements, warranty and lifespan;
- Operational information including sample processing/pre-processing requirements, time requirements, downtime between runs, cleaning/decontamination requirements, consumables required, ease of use and training requirements;
- Results/validation including reporting format, Dx sensitivity and specificity, error margin and detection range;
- Regulatory approval status including platform, other Dx devices manufactured by the company, clinical assay and patents;
- Technology readiness level including stage of readiness, availability of platform as a hand-held device, willingness to adopt new Dx assays for the platform;

- Partnerships including willingness to partner in new assay development and type of partnership;
- Additional information including peer-reviewed literature, key advantages of platform and any additional comments.

The survey was reviewed by DRDC – Suffield Research Centre SMEs prior to dissemination to the vendors by the contractor. Follow-up with vendors that did not respond to the survey was done by the contractor. All surveys received were evaluated and included in the report. In total, 38 vendors replied to the survey (17.7% response). Of these, seven vendors did not wish to participate or provide information about their platforms, three vendors did not feel that their platform would be suitable for the needs outlined by DRDC – Suffield Research Centre, one vendor indicated that their platform was too early in development, and 27 vendors provided information about their platforms. In total, 178 vendors did not respond to the survey invitation or to follow-up.

3.2 Survey analysis

The information provided by the vendor in the survey questionnaire was weighted by the contractor based on the applicable setting (Table 1) and evaluated using the IBM® Statistical Packages for Social Sciences (SPSS) software, Version 19.

Table 1: *Contractor evaluation criteria and weighting.*

Criteria	Parameters included	Weighting	
		Field hospital / FOB	Hand-held/ Field-use
Portability	Dimensions; Weight	10%	10%
Throughput	Single/multiplexed (sample, tests per sample run); Time-to-result; Level of automation	10%	5%
Signature	Sounds; Lights; Thermal output	5%	10%
Ease of use	Training duration; Skills required	10%	10%
Operational timing	Time to begin testing; Downtime; Steps to perform analysis	10%	10%
Operational conditions	Temperature range; Humidity limitations; Elevation	5%	10%
Maintenance / Lifespan	Maintenance frequency; Lifespan of platform; Warranty	10%	5%
Consumables	Requirements; Storage requirements; Shelf life	10%	10%
System requirements	Electricity; Water; Gas; Battery capability, Duration of charge (time/tests)	10%	10%
Samples	Volume required; Types of biological samples; Environmental sample capability	10%	10%
Technical readiness level	Commercialized; Clinical, Pre-clinical, Investigational, Developmental	5%	5%
Publications	Cited in peer reviewed literature	3%	3%
Regulatory	Approved, Submitted	2%	2%
Information extracted from [6].			

Some information provided by the vendors relating to efficacy, results reporting and associated costs were highly variable based on platform development and were often assay dependent. Comments were also provided by vendors related to willingness to adopt new assays and partnership opportunities. This un-weighted information was subjectively considered and utilized by the contractor in determining the top five potential platforms for each setting.

3.3 Survey interpretation

The contractor identified 18 systems that were considered suitable for field hospital / FOB use (Annex A.1), eight that were considered suitable for hand-held/field-use (Annex A.2), and three that were eliminated from the review as they were more suitable for use in a research or Dx laboratory.

Dx platforms were included in the assessment regardless of the type of biomarker that could be detected, the assay, or the assay detection method. Assay methods included immunological or genetic (amplification of NA or NA hybridization). Five vendors indicated that their system used immunological assays exclusively, 12 used genetic assays exclusively, with nine systems capable of using both types of assays (Annex A.3).

Detection methods included optical techniques, EC techniques, colourimetric techniques, or a combination thereof (Annex A.3). Sixteen vendors indicated that their system used optical detection exclusively; three vendors indicated that their system used EC detection exclusively; three vendors indicated that their system could use both optical and EC detection; one vendor indicated their system could use optical, EC or colourimetric detection; and, three vendors indicated that their system used colourimetric detection exclusively.

The contractor identified the top five candidate Dx platforms suitable for field hospital / FOB and the top five candidates suitable for hand-held/field-use applications. Factors that impacted the contractor's top five ranking included: criteria scores obtained from statistical analysis, platform and assay cost, and presence of an open or closed system. Open or closed systems refers to assays, reagents, and consumables being sourced from a variety of companies (open) instead of being sourced from the platform vendor (closed); open systems being advantageous from a cost and supply perspective. Field hospital / FOB platforms that had the ability to be modified to a hand-held format or the ability of being powered by battery in the event of a power outage were scored higher than those that did not have this capability.

3.3.1 Field hospital / FOB setting

The top five platforms suitable for field hospital / FOB use, as determined by the contractor, are listed in Table 2. Scoring from evaluation of parameters listed in Table 1 was not a direct indication of the final ranking. For example, Fraunhofer IZI-BB IVD Platform had a score of 76.2 and was ranked third, whereas both Ziplex System and MAGPIX Instrument had lower scores, but were ranked first and second, respectively. This was due to consideration of unweighted factors, such as cost, multiplexed assays, and the option for battery power, for example.

Table 2: *Top five diagnostic platforms suitable for use in a field hospital / FOB as identified in the contract report.*

Rank	Platform	Score	Ranking Characteristics																	
			Portability	Low sample volume	Variety of sample types	Detection of proteins and nucleic acids	Low unit cost	Low test cost	Multiplexed assays	Commercialized	Option for battery power	Operational signature	Temperature range of operations	Automated	Rapid test set-up	Rapid time-to-result	Integrated sample processing	No additional equipment needed	Long lifespan	Low maintenance requirements
1	Ziplex System	65.6	✔	✔	✔	✔	✔	✔	✔		✔		✔		✔			✔		
2	MAGPIX Instrument	55.7		✔	✔	✔			✔	✔						✔ ^			✔	
3	Fraunhofer IZI-BB IVD Platform	76.2	✔	✔	✔	✔	✔	✔			✔			✔		✔ @			✔	✔
4	T-COR 8	70.3	✔		✔	X*			✔		✔	✔	✔			✔ #	✔			
5	GenePOC Inc. Diagnostic System	69.7		✔	✔	X*			✔							✔ #	✔			✔

*only detect nucleic acids; time-to-result: @ 15 min, # <1 h, ^ 90 min.
Information extracted from [6].

3.3.2 Hand-held/field-use setting

The top five platforms suitable for hand-held/field-use, as determined by the contractor, are listed in Table 3. Scoring from evaluation of parameters listed in Table 1 was not a direct indication of the final ranking. For example, Mycrolab Diagnostics had a score of 69.0 and was ranked third, whereas both HRDR-200 and AgPlus Advantage had higher scores, but were ranked fourth and fifth, respectively. This was due to consideration of unweighted factors, such as cost, flexibility of assay format, and presence of a barcode scanner, for example.

Table 3: *Top five hand-held diagnostic platforms as identified in the contract report.*

Rank	Platform	Score	Ranking Characteristics												
			Portability	Low sample volume	Variety of sample types	Detection of proteins and nucleic acids	Low cost	Multiplexed assays	Commercialized	Rechargeable battery	Long battery life	Flexible assay format	Operational signature	Temperature range of operations	Barcode scanner available
1	TrueDX	78.6	✔	✔	✔	✔	✔	✔	✔						
2	iDiagnostics	75.6	✔		✔	✔					✔	✔	✔		
3	Mycrolab Diagnostic Platform	69.0	✔		✔	✔		✔		✔					
4	HRDR-200[#]	72.8								✔	✔			✔	
5	AgPlus Advantage	72.9	✔	✔	✔	X*				✔	✔				✔

*does not detect nucleic acids; [#] Smartphone reader for hand-held assays.
Information extracted from [6].

4 DRDC – Suffield Research Centre analysis of market place survey results

4.1 Survey response rate

In determining the adequacy of a response rate to a survey, it is important to determine the intent of the survey, for example, is the purpose of the survey to gain insight about a particular subject or to enable generalizations to be made to a larger population? Survey response rates should be higher when the data obtained is used to make generalizations to the larger population than when it is used to obtain information [18]. This survey was designed to obtain information about Dx platforms that have potential applications for biomarker detection in settings specific to the CAF, thus even though the response rate obtained from the contractor survey (17.7%) was low, the responses were informative and were of great benefit in establishing a baseline portfolio of potential Dx platforms and vendors, as well as assessing general trends.

4.2 Comparison of features of diagnostic platforms for field hospital and field-use identified by DRDC – Suffield Research Centre SMEs and the contractor

A review of the contractor's report by DRDC – Suffield Research Centre SMEs identified a few features that were considered to be more important to the contractor than to DRDC – Suffield Research Centre SMEs. These included platform cost and adaptability to a hand-held format for field hospital / FOB use. In addition, DRDC – Suffield Research Centre SMEs identified several parameters having higher importance for the CAF than those identified by the contractor. These included multiplexing capability and integrated sample processing. These differences are discussed further in this section.

The biomarkers being studied in the biomarker project are NA, specifically ribonucleic acid (RNA), and potentially protein. Thus candidate Dx platforms must, at minimum, be able to detect NA, but would score higher if they were capable of detecting both NA and protein on the same platform.

Dx platforms that are capable of running multiple assays on a single sample at the same time are strong candidates because studies have indicated that the determination of whether an individual is infected prior to symptom development will require running tests against multiple different biomarkers at the same time. Biomarker panels containing between four and 50 different biomarkers have been shown to discriminate between individuals with and without a particular condition [5, 9–14].

The Dx platform should ideally be able to process multiple specimen types including, but not limited to, blood, serum, urine, saliva and swab samples, and sample processing should ideally be integrated into the Dx platform to minimize exposure of personnel to potential infectious agents and decrease risk of sample cross-contamination.

A faster time-to-result (time from initiation of sample handling until a result is obtained) is preferred in order to be able to identify and initiate treatment or impose quarantine as soon as possible after exposure in order to achieve mission success.

Platform cost was not deemed to be a critical component of the evaluation by DRDC – Suffield Research Centre SMEs; however, availability of open source reagents and assays for the Dx platform was deemed to be critical, since this usually results in a lower cost/test and a more robust supply network of consumables.

Table 4 details the evaluation criteria that were ranked differently between the contractor and the DRDC – Suffield Research Centre SMEs. Table 5 details the scoring system used by the DRDC – Suffield Research Centre SMEs for ranking the different platforms.

Table 4: *Comparison of the relative importance of various criteria used in evaluation of Dx systems by DRDC – Suffield Research Centre SMEs and the contractor.*

Parameter	**DRDC – Suffield Research Centre**	**Contractor**
Analysis of protein and NA on same platform	Higher	Lower
Analysis of wide variety of sample types	Higher	Lower
Assay cost	Lower	Higher
Battery power (field hospital / FOB use)	Higher	Lower
Integrated sample processing	Higher	Lower
Modifiable to hand-held (field hospital / FOB use)	Lower	Higher
Multiplexing	Higher	Lower
Platform cost	Lower	Higher
Publications	Lower	Higher
Time-to-result	Higher	Lower
Utilization of open source reagents	Higher	Lower
Commercialized	Higher	Lower

Table 5: *Scoring system used by DRDC – Suffield Research Centre SMEs.*

Criteria for field hospital / FOB setting and field-use setting		
Criteria	**Response**	**Score**
Sample processing	Integrated	6
	Some pre-processing required	2
	Pre-processing required	0
Samples type	Various	3
	Single sample type	0
Analyte detected	NA + protein	6
	NA (in development) + protein	3
	NA	3
	Protein	1
System	Open	2
	Closed	0
Commercialized	Yes	2
	No	0
Multiplex assays	10+ assays/sample	4
	4–9 assays/sample	2
	2–4 assays/sample	1
	1 assay/sample	0
Time-to-result	≤30 min	4
	30–60 min	1
	>60 min	0
Immunoassay	Yes	1
	No	0
Genetic	Amplification	2
	Hybridization	1
Detection	Optical	1
	Colourimetric	3
	Electrochemical	4
Additional criteria for field hospital / FOB setting		
Availability of being battery powered	Yes	2
	No	0

4.3 Top diagnostic platform candidates identified by DRDC – Suffield Research Centre SMEs

4.3.1 Field hospital / FOB setting

Platforms that have integrated sample processing (automated sample processing built into the device without a hands-on requirement) are desirable so as to minimize sample handling and processing, reduce contamination risk to the operator, and reduce operator error. Of the eighteen platforms identified in the contractor survey as being suitable for use in a field hospital / FOB (Annex A.1), nine did not require sample pre-processing prior to sample analysis. Of those, two were only designed to be used with swab samples, limiting their versatility and thus were removed from further consideration for selection of the top technologies. The remaining seven platforms with integrated sample processing had the capability to process various sample types and could detect NA. Four of these could also detect proteins. These four Dx platforms (Table 6) are considered by DRDC – Suffield Research Centre SMEs as having the best potential of the 18 identified field hospital / FOB platforms for the operationalization of Dx assays targeting pre-symptomatic biomarkers of infection. Only one of these four (Fraunhofer IZI-BB IVD platform) was identified as a top five candidate in the contract report. The other platforms identified in the contractor top five list (Table 2) did not have integrated sample processing and, additionally, two did not have a capability to detect proteins, which could limit future assay development for pre-symptomatic biomarkers of infection.

The first three platforms listed in Table 6 can handle multiple tests/sample/run; have a time-to-result of 20 min or less; have integrated sample processing; accept various types of samples; and utilize open sourced reagents. Of note, all the systems in Table 6 utilize EC detection methods, either alone or in conjunction with optical detection (fluorescence). DNA is readily detected by all four platforms, but detection of RNA is listed as "feasible".

Table 6: *Dx platforms with potential use for biomarker detection in field hospital / FOB settings as determined by DRDC – Suffield Research Centre SMEs.*

Platform	Sample processing	Sample type	System	# Tests/ sample	Time-to-result	Assay	Detection	Comments
Fraunhofer IZI-BB IVD Platform[abc]	Integrated	Various	Open	10	10–15 min	Ab, Hyb	FL, EC	Developmental
pTDi*[abc]	Integrated	Various	Open	5	20 min	Ab, PCR	FL, EC	
CapSenze 100[ab]	Integrated	Various	Open	32	15 min	Ab, Hyb	EC	Regulatory application in preparation
NESDEP IU*[ab]	Integrated	Various	Closed	1	60 min	Hyb	EC	In clinical trials, more extensive instrument set-up required

* Platform is commercialized; Analyte detected: [a] proteins, [b] nucleic acids, [c] metabolites; Assay: Ab (immunological, Ab-Ag), PCR, or Hyb (hybridization, non-amplification genetic detection); Detection: FL (fluorescence optical system), EC (electrochemical system).

4.3.2 Hand-held/field-use setting

Eight platforms were identified in the contractor survey as having the potential for use as a hand-held/field-use device (Annex A.2); however, one was a reader only and was therefore removed from consideration (HRDR-200). Another (BD Veritor) was designed to be used with swabs only, limiting its versatility and thus eliminating it from consideration. Three vendors indicated that their platforms could detect both NA and proteins, and a fourth indicated that detection of DNA on their platform was in development. All four platforms (Table 7) had the capability to use various sample types and had little or no sample pre-processing requirements. These four platforms are considered by DRDC – Suffield Research Centre SMEs as having the best potential of the eight platforms for the operationalization of Dx assays targeting pre-symptomatic biomarkers of infection on hand-held devices for field-use. All four platforms were in the top five list of candidates identified in the contract report. Of note, the TrueDx system is commercialized and currently has two assays (one for thyroid stimulating hormone, and one for prostate specific Ag) that are approved by the U.S. Food and Drug Administration (FDA). Also of note, EC detection is used by three of the top four hand-held/field-use platforms, highlighting the importance of EC detection in current industrial hand-held system designs.

Table 7: *Dx platforms with potential use for biomarker detection in hand-held/field-use settings as determined by DRDC – Suffield Research Centre SMEs.*

Platform	Sample processing	Sample type	System	# Tests/ sample	Time-to-result	Assay	Detection	Comments
iDiagnostics[abc]	Some pre-processing	Various	Open	32	Info not given	Ab, Hyb	FL	Developmental
Mycrolab Diagnostic Platform[abc]	None	Various	Open	8	30–60 min	Ab, PCR	FL, EC	Developmental
TrueDX*[abcd]	Pre-processing for NA; None for protein	Various	Closed	12	15 min	Ab, Hyb	C,FL,EC	Some assays are FDA approved
AgPlus Advantage[ad#]	Some pre-processing	Various	Closed	5	10–15 min	Ab	EC	Investigational

* Platform is commercialized; Analyte detected: [a] proteins, [b] nucleic acids, [c] metabolites, [d] hormones, [#] limited work with DNA; Assay: Ab (immunological, Ab-based), PCR, or Hyb (hybridization, non-amplification genetic detection); Detection: FL (fluorescence optical system), C (colourimetric), EC (electrochemical system).

5 Conclusion

The contract report examined Dx systems and identified a number of platforms that were potentially suitable for operationalization of Dx assays targeting pre-symptomatic biomarkers of infection in a field hospital / FOB and hand-held/field-use setting. A review of these platforms by DRDC – Suffield Research Centre SMEs identified four promising platforms for each setting. The majority of these utilize EC biosensor detection technology. EC sensors are easily miniaturized and cost effective due to the simplicity of the electrodes that are used in the sensors [15]. EC biosensor technology therefore lends itself well to hand-held devices which have a requirement to be small, light-weight, and robust [19, 20]. EC detectors are currently used in the medical arena for determination of blood oxygen and glucose levels [15], however, although EC detection of DNA is well documented, EC detection of RNA is less so.

Although this market survey did not identify any Dx platforms that are well advanced in detecting RNA using EC, it provided a reasonable assessment of current platforms that have the potential to operationalize assays developed for pre-symptomatic biomarkers of infection, and that could be used in a field hospital / FOB or in a hand-held/field-use setting. The low survey response may have limited the field of potential EC biosensor systems that could otherwise be of interest for future assessment. For example, the following EC-based systems were not identified in the market survey: Abbot which manufacturers the iSTAT1 system, a commercialized hand-held system for point-of-care testing for glucose, electrolytes, cardiac markers, hematology and blood gases; CH Instruments, Inc. which manufacturers both laboratory and hand-held EC detectors; GeneFluidics Inc. which manufactures the Helios[1] and Proteus Robotic System instruments; and Metrohm Autolab B.V., which manufactures various EC detectors, at least one of which has been shown to detect DNA [22]. Other unidentified EC systems such as these, may in time, be identified and added to the list of potential systems worth considering as pre-symptomatic Dx platforms.

EC biosensor technology needs to be studied with respect to other established detection technologies and a number of performance-related parameters evaluated before it can be accepted with confidence for pre-symptomatic Dx, including:

- optimization of the functional surface for immobilization of the capture molecule;
- optimization of capture and detection probe composition, concentration, and orientation;
- optimization of assay conditions;
- evaluation of Dx sensitivity and Dx specificity of assays; and
- evaluation of limits of detection and assay range.

DRDC – Suffield Research Centre is currently soliciting bids for evaluation of EC biosensors for detection of RNA, to determine if the technology is sensitive and specific enough to be used for Dx, specifically for pre-symptomatic identification of infected individuals. The initial focus will be on the evaluation of the technology for detection of specific RNA molecules in simple and

[1] The Helios system was critically evaluated for DRDC – Suffield Research Centre under contract for pathogen immunoassay detection [21].

complex matrices (e.g., buffer and blood, respectively) using a research laboratory based system. Should the technology demonstrate that it is sufficiently sensitive for detection of specific RNAs, additional work will be done to develop assays for biomarkers that can be used on an EC-based platform suitable for use in a field hospital / FOB setting. This setting is to be evaluated prior to evaluation of EC-based hand-held/field-use platforms since systems used in more "advanced" settings typically allow for greater flexibility in system design. Following this evaluation, if specific biomarkers of infection can be detected with sufficient sensitivity, specificity and predictive value using assays run on EC-based platforms suitable for field hospital / FOB use, the winning contractor will evaluate these assays on a candidate hand-held EC-based system.

Although, most of the EC-based Dx platforms are still in development, two of the platforms identified by DRDC – Suffield Research Centre SMEs as having potential for use in a field hospital / FOB either have a regulatory application in process or are undergoing clinical trials, and one of the platforms identified as being potentially useful as a hand-held/field-use device has assays that are approved by the FDA. Additionally, a commercialized hand-held EC system (iSTAT1) that is currently being used for clinical point-of-care testing was not identified in the contract report although the manufacturer of that system was contacted by the contractor to participate in the survey. The emergence of EC technology being commercially developed for Dx applications demonstrates this technology as a viable option for pre-symptomatic Dx should EC technology prove to be sensitive enough to detect specific biomarker molecules.

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Annex A Platform information

A.1 Platforms suitable for use in a field hospital / FOB

Table A.1: *Platforms suitable for use in a field hospital / FOB.*

Platform[a]	Sample processing	Sample type	Analyte detected[b]	System	Commercialized	Capable of:		Cost		DRDC-SME Score
						Modification to handheld	Battery powered	Unit	Test	
Fraunhofer IZI-BB IVD Platform	Integrated	Various	abc	Open		✔	✔	$7,000	$3–$7	27
CapSenze 100	Integrated	Various	ab	Open			✔	$51,200	$10 + consumables	27
pTDi	Integrated	Various	abc	Open	✔	✔		$67,700	$14–$135	25
NESDEP IU	Integrated	Various	ab	Closed	✔		✔	$50,000	$25–$50	20
Ziplex System	Some pre-processing	Various	ab	Open		✔	✔	$5,000	$5–$10	20
PanNAT System	Integrated	Various	b	Closed			✔	$30,000	$40–$100	19
FilmArray	Integrated	Various	b	Closed	✔			$50,000	$180	19
MAGPIX Instrument	Some pre-processing	Various	abc	Open	✔			$35,000	$240	19
cobas Liat	Integrated	Swabs only	b	Closed	✔			Not provided	Not provided	16
Accutas	Integrated	Various	b	Closed				$5,000	Not provided	16
T-COR 8	Some pre-processing	Various	b	Open			✔	$28,500 USD	$35–$65 USD	15
LuBEA	Some pre-processing	Various	ab	Closed				$14,000	Not provided	15
Spartan RX	Integrated	Swabs only	b	Closed	✔			$9,995	$150	13
MOL 1001	Some pre-processing	Various	b	Open	✔			$60,000	$50–$80	13
Lightcycler 2.0	Pre-processing	Various	b	Open	✔			$95,000	$10	12
GenePOC Inc. Diagnostic System	Some pre-processing	Various	b	Closed				$20,000	$15–$20	12
geneLEAD1	Some pre-processing	Various	b	Closed				$19,000	$10	10
BD Accuri C6 Flow Cytometer	Pre-processing	Various	a	Open				$56,000	$2–$22	8

[a] Blue font indicates best Dx platforms identified by DRDC – Suffield Research Centre SMEs; yellow shading indicates top 5 platforms as identified in the contract report; grey shading indicates top responses in the category.
[b] a = proteins, b = nucleic acids, c = metabolites.
Information extracted from [6].

A.2 Hand-held platforms suitable for use in the field

Table A.2: *Hand-held platforms suitable for use in the field.*

Platform[a]	Sample processing	Sample type	Analyte detected[b]	System	Commercialized	Cost		DRDC-SME Score
						Unit	Test	
iDiagnostics	Some pre-processing	Various	abc	Open		$9,800 USD	$0.10–$1.00 USD	21
TrueDX	Pre-processing	Various	abcd	Closed	✔	$4,500 USD	$10 USD	19
Mycrolab Diagnostic Platform	Some pre-processing	Various	abc	Open		Not provided	$5–$50 USD	16
AgPlus Advantage	Some pre-processing	Various	ad#	Closed		~$5,800 CAD	~$11.00 CAD	14
two3	Some pre-processing	Various	b	Open		$7,500 USD	$10–$70	13
Rapid Multi-line Assay	Some pre-processing	Blood	a	Open	✔	Not provided	$10	13
BD Veritor	Some pre-processing	Swabs only	a	Closed	✔	$399	$5.50–$15	10
HRDR-200	N/A[c]	N/A	ac	Closed		$1,400 USD	Variable	5

[a] Blue font indicates best Dx platforms identified by DRDC – Suffield Research Centre SMEs; yellow shading indicates top 5 platforms as identified in the contract report; grey shading indicates top responses in the category.
[b] a = proteins, b = nucleic acids, c = metabolites, d = hormones, # = limited work with DNA. [c] Not applicable, reader only.
Information extracted from [6].

A.3 Assay and detection methods of the various platforms

Table A.3: *Assay and detection methods of the various platforms.*

Platform	Assay Method			Detection Method				DRDC-SME Score
	Immuno-logical	Genetic		Optical		Colour-imetric	Electro-chemical	
		Amplification	Hybridization	Fluorescence	Chemi-luminescence			
Field hospital / FOB								
pTDi*[abc]	✔	✔		✔			✔	8
Fraunhofer IZI-BB IVD Platform[abc]	✔		✔	✔			✔	7
CapSenze 100[ab]	✔		✔				✔	6
NESDEP IU*[ab]			✔				✔	5
Ziplex System[ab]	✔	✔			✔			4
T-COR 8[b]		✔		✔				3
GenePOC Inc. Diagnostic System[b]		✔		✔				3
Spartan RX*[b]		✔		✔				3
cobas Liat*[b]		✔		✔				3
PanNAT System[b]		✔		✔				3
MOL 1001*[b]		✔		✔				3
Lightcycler 2.0*[b]		✔		✔				3
Accutas[b]		✔		✔				3
geneLEAD1[b]		✔		✔				3
FilmArray*[b]		✔		✔				3
LuBEA[ab]	✔		✔		✔			3
MAGPIX Instrument*[abc]	✔		✔	✔				3
BD Accuri C6 Flow Cytometer[a]	✔			✔				2
Hand-held/field-use								
TrueDX*[abc]	✔		✔	✔		✔	✔	10
Mycrolab Diagnostic Platform[abc]	✔	✔		✔			✔	8
AgPlus Advantage[ad#]	✔						✔	5
iDiagnostics[abc]	✔		✔	✔				3
two3[b]		✔		✔				3
Rapid Multi-line Assay*[a]	✔					✔		4
BD Veritor*[a]	✔					✔		4
HRDR-200[ac^]	✔					✔		4

Blue font indicates best Dx platforms identified by DRDC – Suffield Research Centre SMEs; yellow shading indicates top 5 platforms identified in the contract report;
* Platform is commercialized; [a] proteins, [b] nucleic acids, [c] metabolites, [d] hormones, # limited work with DNA; ^ reader only.
Information extracted from [6].

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List of symbols/abbreviations/acronyms/initialisms

Ab	Antibody
Ag	Antigen
BT	Biothreat
CAF	Canadian Armed Forces
DNA	Deoxyribonucleic acid
DRDC	Defence Research and Development Canada
Dx	Diagnostic
EC	Electrochemical
FDA	U.S. Food and Drug Administration
FOB	Forward operating base
H	Hours
HHA	Hand-held assay
Min	Minutes
NA	Nucleic acid
PCR	Polymerase chain reaction
R&D	Research and Development
RNA	Ribonucleic acid
S&T	Science and Technology
SME	Subject matter experts

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Defence Research and Development Canada – Suffield Research Centre (DRDC – Suffield Research Centre) has a project examining the suitability of using host-specific factors (biomarkers) as an indication of infection, prior to symptom development in an exposed individual. Should suitable biomarkers be identified following rigorous examination to ensure that they are specific to infection and sensitive enough to be useful, assays for these biomarkers will need to be transitioned from the research laboratory to the Canadian Armed Forces (CAF). Diagnosis of infection with a pathogen, prior to symptom development, could aid the CAF in screening individuals or groups that need to be treated, isolated, or returned to normal duties. During deployment, diagnosis of CAF members exposed or suspected of being exposed to serious pathogenic agents would be done by medical staff in a field hospital or at a forward operating base (FOB), or in the field by the operators themselves in order to identify at-risk individuals or at-risk populations. In order for any diagnostic (Dx) test to be useful under these conditions, the Dx equipment must, at minimum, have a relatively small footprint; have limited consumables and power requirements; and be relatively easy to operate, with minimal maintenance and minimal operator training burden. In order to identify Dx platforms that could meet these requirements, DRDC – Suffield Research Centre initiated a contract to survey Dx platform vendors, and identify Dx platforms that could potentially meet these requirements. This report outlines the key findings from the contract report as it pertains to identifying Dx platforms that could be suitable for detection of biomarkers in a field hospital / FOB setting and hand-held platforms that could be used by operators in the field; a critical evaluation of the contractor's findings by DRDC – Suffield Research Centre subject matter experts (SMEs); and a plan to exploit the findings identified in this report.

Le Centre de recherches de Suffield de Recherche et développement pour la défense Canada (RDDC – Centre de recherches de Suffield) mène un projet qui porte sur la pertinence d'utiliser des facteurs propres à un hôte (biomarqueurs) comme indicateur d'infection, avant l'apparition des symptômes, chez un sujet exposé. Si un examen rigoureux permet de définir les biomarqueurs pertinents propres à une infection et suffisamment sensibles pour être utiles, il faudra transférer les analyses de ces biomarqueurs du laboratoire de recherche aux Forces armées canadiennes (FAC). Un diagnostic d'infection par un agent pathogène, avant l'apparition des symptômes, pourrait aider les FAC à déterminer s'il faut traiter ou isoler une personne ou un groupe de personnes, ou bien si on peut permettre la reprise des fonctions habituelles. Au cours des déploiements, le diagnostic des membres des FAC qui ont été exposés à un agent pathogène dangereux, ou qu'on soupçonne de l'avoir été, serait établi par le personnel médical dans un hôpital de campagne ou sur une base d'opérations avancée (BOA), ou encore par les utilisateurs eux-mêmes sur le terrain. Cela permettrait de déterminer les personnes ou les populations à risque. Pour qu'un test de diagnostic soit utile dans de telles conditions, l'équipement de test doit, à tout le moins, être relativement peu encombrant, exiger peu de produits consomptibles et d'électricité, et être relativement facile à utiliser, sans nécessiter trop d'entretien ni de formation pour les utilisateurs. RDDC – Centre de recherches de Suffield a attribué un contrat afin de sonder les fournisseurs de plateformes diagnostiques pour déterminer lesquelles pourraient satisfaire à ces exigences. Le présent rapport donne un

aperçu des principales conclusions tirées du rapport de contrat en ce qui a trait à la recherche de plateformes diagnostiques pouvant servir à la détection des biomarqueurs dans un hôpital de campagne ou une BOA et de plateformes portatives pour les utilisateurs sur le terrain une évaluation critique des conclusions de l'entrepreneur par des experts en la matière de RDDC – Centre de recherches de Suffield. Un plan visant à tirer profit des conclusions présentées figure également dans le rapport.

14. KEYWORDS, DESCRIPTORS or IDENTIFIERS (Technically meaningful terms or short phrases that characterize a document and could be helpful in cataloguing the document. They should be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location may also be included. If possible keywords should be selected from a published thesaurus, e.g., Thesaurus of Engineering and Scientific Terms (TEST) and that thesaurus identified. If it is not possible to select indexing terms which are Unclassified, the classification of each should be indicated as with the title.)

diagnostic platforms; biomarkers; pre-symptomatic; forward operating base; field hospital; hand-held; field-use