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Deployment of a full clinical laboratory capability to support enhanced clinical care in an Ebola treatment unit in Sierra Leone

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Abstract

In November 2014 the UK's Centre of Defence Pathology established a full clinical laboratory at Kerrytown in Sierra Leone providing haematology, biochemistry, coagulation, microbiology and transfusion services to enable enhanced supportive care of patients with Ebola Virus Disease and those presenting with other conditions. The delivery of such a range of diagnostic tests, to be conducted on blood containing a Hazard Group 4 pathogen in a field environment, was unique. This novel capability and associated containment facilities were planned and delivered in a matter of weeks and provided over 3500 diagnostic tests and 200 blood components from November 2014 to June 2015. The laboratory is recognised as having been a critical enabler of delivery of a high standard of clinical care and the challenges and issues faced, along with the solutions and successes are described.

Introduction

In December 2013 an outbreak of Ebola Virus Disease (EVD) began in Guinea and subsequently spread to neighbouring countries in West Africa including Sierra Leone (SL). In total the outbreak affected 28,616 people and led to 11,310 deaths of which 3,589 were in SL [1]. In the summer of 2014 a United Kingdom (UK) response to the EVD outbreak in SL was announced which required the deployment of a significant number of UK nationals to the country. Due to the limited medical support available in SL a requirement was identified for a medical facility to be deployed which could offer international and local healthcare workers (HCWs) assurance of an enhanced level of supportive care, not otherwise available in SL, should they become infected with Ebola virus (EBOV) [2].

In August 2014 the UK Defence Medical Services (DMS) were tasked to deliver a 12-bed EVD treatment unit (EVDTU) for the diagnosis and management of international and local HCWs suspected of having EVD. In order to provide the high standard of care required, provision of full laboratory support to this facility was deemed essential.

Background and mission

EBOV is classified as a Hazard Group 4 pathogen and in accordance with UK guidelines should be handled within a Containment Level 4 (CL4) laboratory [3]. The UK military has well established training, equipment and plans for the deployment of clinical support to a wide range of medical situations; however at the time there was no laboratory capability to deliver the necessary requirements to handle significant numbers of clinical samples potentially containing EBOV.

There was an overarching requirement to provide assurance to the deployed international personnel, local aid workers and other medical staff that they would receive a high standard of medical care should they require it, which would encourage them to deploy and continue to work throughout the outbreak. The Centre of Defence Pathology (CD Path), the specialist team within the Royal Centre for Defence Medicine responsible for the organisation, training and operational delivery of pathology services to the UK DMS, was tasked to deliver a UK-standard clinical laboratory facility to meet this requirement, by supporting the medical missions of both the military facility and the co-located 80-bed EVDTU staffed by a non-governmental organisation (NGO).

Method

In order to fulfil its mission, CD Path was required to define the requirement, identify and procure equipment to provide the laboratory capability needed, provide appropriate training and then run the facility. CD Path was tasked to provide manning for the clinical laboratory service, as well as the necessary governance and assurance.

Defining the requirement

In mid-2014 no evidence was available that described the delivery of similar laboratory support to a Hazard Group 4 organism outbreak. The handling of such organisms is normally associated with specialist laboratories that have additional protection measures to mitigate the threat of the transmission to laboratory staff and the wider community.

Guidance provided to all UK hospitals [4] permitting initial diagnostics to be performed on patients presenting with symptoms

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consistent with a suspected viral haemorrhagic fever (VHF) was reviewed, however the risk analysis determined the threat to be very different when delivering laboratory support to the management of known EVD patients.

The UK's clinical centre for management of VHF, the Royal Free Hospital in London, has a significant laboratory capability benefiting from substantial infrastructure including a HEPA filtered air environment and bespoke changing and decontamination facilities, designed to process a low number of clinical samples. Unfortunately these same features, whilst representative of the UK standard of care, meant this laboratory was not an ideal model on which to base a rapidly deployable unit to the field. However, several principles from the facility and its practices were incorporated in the generation of a robust and deliverable solution.

Laboratory facilities

Given that the delivery of a full CL4 laboratory was unachievable in a rapid deployment field setting, two options were explored to determine how laboratory support could most safely and effectively be delivered:

Option 1 - Locate the laboratory within the Red Zone

Situating the laboratory within the Red Zone (defined as the clinical area in which suspected and confirmed cases of EVD were managed) offered the advantages of specimens being easily transported to the laboratory with no requirement for sample decontamination. Analysers currently used by the UK DMS capable of high sample throughput and rapid delivery of results could be utilised, reducing the pre-deployment training burden and supply chain issues.

However, full Personal Protective Equipment (PPE) would be required to be worn by the Biomedical Scientist (BMS), with resulting physiological degradation significantly limiting the amount of time the laboratory would be able to operate.

Option 2 - Locate the laboratory outside of the Red Zone in a dedicated building

With this option, the sample analysers would be operated inside an isolator protecting the operator from EBOV. Without the requirement for PPE, reduced degradation for the laboratory staff meant the laboratory could work longer hours in safer working conditions, resulting in increased access to the laboratory repertoire.

However, specimen management would be much more challenging, requiring the development of a safe packaging and decontamination process for specimen transportation from the Red Zone to the laboratory, with a subsequent lengthening of processing time and delivery of result.

Furthermore, none of the then in-service analysers were suitable for use inside an isolator due to their size or design, which prevented safe access, and therefore the procurement of smaller analysers would be required, as well as appropriate isolators.

Option 2 was selected as this was deemed the safest for staff and enabled greatest availability of laboratory support, whilst tolerating the effect on time to results. A flexible film type of isolator was chosen based on ease of assembly, use and the lead-time for delivery. Due to lack of experience of the use of large flexible isolators in DMS, expert advice was sought from Public Health England (PHE) in selecting, procuring and maintaining the isolator.

A laboratory area adjacent to, but just external to the Red Zone, had already been built at Kerrytown and as PHE had been tasked to provide a capability for diagnosing EBOV [5] there was an opportunity to have a single PHE and military laboratory which combined the planning, training and use of common standard operating procedures (SOPs) to provide an optimal working environment.

Laboratory capability

During the planning phase a description of the delivery of laboratory support to an EVD patient in the United States was published [6]. This description supported the planning assumptions made by CD Path and reiterated the expectation of provision of a high standard of care which would require a comprehensive and robust laboratory capability, offering a full repertoire of tests (Table 1).

Analysers

The greatest challenge to developing the capability was identifying and sourcing suitable analysers that fulfilled specific requirements including:

- Offering an appropriate range of tests on whole blood, as centrifugation was to be avoided as it is a high-risk procedure when performed on samples containing EBOV.
- Size and operability compatible with the isolator.
- Robust units capable of reliable operation in an austere environment of high ambient temperature and humidity, requiring minimal maintenance as no engineering service would be available.
- Availability with a short supply time (less than 4 weeks).

The following analysers were selected as fulfilling these requirements:

Biochemistry - Abaxis Piccolo Express

- Two cartridges available (Metlac 12 and Amlyte 13) which between them assayed all the key analytes required. (Table 1).
- No requirement for additional reagents.
- Results provided within 15 minutes.

Haematology - Horiba ABX ES60

- Provided a full blood count with three part white cell differential.
- A single reagent pack that also collected the waste by-products allowing easy removal from the isolator.
- Robust and rapid delivery of results.

Coagulation analysis - Hemachron Signature Elite

- Assay of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT).
- A hand held analyser that was unique in that citrated whole blood samples could be analysed within the laboratory without the requirement for centrifugation

Molecular diagnosis - BioFire FilmArray

- Multiplex PCR platform.
- Provides a diagnostic capability for the causes of gastroenteritis, respiratory disease, and septicaemia.
- Very easy to operate with results achieved within in one hour

Table 1. Test repertoire at Kerrytown DMS laboratory indicating clinicians presumed importance pre-deployment..

Test	Importance in management of patients with confirmed Ebola Virus Disease			Importance in management of patients with Pyrexia of Unknown Origin		
	Critical	Required	Desirable	Critical	Required	Desirable
FBC and Diff		Y		Y		
Clotting studies	Y				Y	
Group & Save, Cross match						
Sodium	Y				Y	
Potassium	Y				Y	
Urea	Y				Y	
Creatinine	Y				Y	
Glucose	Y			Y		
Calcium			Y			Y
Magnesium		Y			Y	
Liver Function Tests		Y			Y	
Magnesium			Y			Y
Bicarbonate		Y			Y	
Lactate	Y			Y		
CRP	Y			Y		
HIV / BBV		Y		Y		
Malaria	Y			Y		
Dengue		Y			Y	
Blood Cultures			Y			Y
Serum save	Y			Y		

Blood culture - Biomerieux BacT/ALERT

- Detection of positive blood cultures within hours.
- Used in conjunction with FilmArray to provide rapid identification of the cause of sepsis.

In addition to the analysers, a number of lateral flow rapid tests were used within the isolator e.g Alere determine™ HIV1/2, Binax NOW® Malaria and SD Bioline Dengue Duo®

Point-of-care testing

The laboratory also provided training and oversight for point-of-care testing (POCT) undertaken at the patient bedside in the Red Zone, when the main laboratory was not operating. The DMS in-service analyser (i-STAT Handheld Blood Analyser, Abbott) was evaluated as acceptable to be operated by clinical staff in this environment, and could provide basic blood chemistry, blood gases and coagulation using a range of cartridges.

Blood Transfusion

The requirement to provide blood components was considered an important element in supporting patients with a disease thought to include a significant haemorrhagic component. The DMS has a long and distinguished history of being able to support transfusion around the world to UK standards of regulation [7]. The following blood components were supplied by the Defence Blood Supply Team from the UK using estimates based on the clinical experience of HCWs who had worked in EVDTUs earlier in the outbreak:

- Red Cell Concentrate (RCC)
- Fresh Frozen Plasma (FFP)
- Platelets
- Cryoprecipitate (Cryo)

Routine blood transfusion practice requires the use of centrifugation for blood grouping, antibody screening and compatibility testing. As this was not available, universal blood components, O RCC and AB FFP, were supplied, with O Rhesus (D) negative RCC reserved for females.

The blood component storage facilities were co-located within the air-conditioned pharmacy area to allow the blood banks, plasma freezers and plasma defrosters to operate effectively away from the processing of EBOV samples.

In accordance with UK legislation, there was full traceability of all blood components supplied, and this was achieved with scanned copies of paperwork being stored electronically. To our knowledge, this capability was unique to the EVD outbreak in West Africa.

Pre-deployment training

The training was facilitated by the Army Medical Services Training Centre (AMSTC) in Strensall, York, UK, and included a nine-day package comprising of intelligence, culture and language briefs, media updates, clinical lectures, infection control, and practical elements about the use of PPE.

A near replica of the entire EVDTU, including the laboratory, was constructed in a hanger at AMSTC, providing an excellent environment to undertake training. The analysers were delivered by CD Path and the isolator was provided by PHE Porton Down, whose staff also delivered vital user training in techniques unfamiliar to DMS personnel. Specific equipment training was delivered by the BMS Training Team from the Defence College of Healthcare Education and Training (DCHET) from DMS Whittington, with additional assistance provided by Horiba UK for the haematology analyser.

SOPs covering all areas pertaining to the laboratory, including the movement of specimens from the Red Zone and decontamination and spillage procedures, were developed at AMSTC with specialist advice from PHE. All SOPs were tested and validated before deployment and the training package culminated in a combined assessed exercise during which all elements of the facility were comprehensively tested through a variety of clinical, administration, technical and ethics-based

scenarios. In addition, SOPs were also tested in theatre to ensure they were fit for purpose *in situ* before work commenced.

Manning

The clinical laboratory service was provided by four military biomedical scientists (BMS), which represented a doubling of the proposed manning from the initial planning stages based on a military capability of this size. Staff deployed for 8 weeks at a time in tranches. This number of BMSs increased to five for Tranche 3 to enable more robust access to the laboratory and improved laboratory management. The manning was reduced by the military to three on Tranche 4 when the overall capability of EVDTU reduced from 12 to 8 beds. Given that the main constraint for personnel was the requirement to operate in buddy-buddy pairs at all times, this reduction in numbers severely affected the capability of the laboratory. The effect on rest time available, and the consequent impact on individuals working in such an intense, laborious and challenging environment, illustrated the weakness of a 'one size fits all' planning assumption.

Deployments were limited to 60 days to reduce performance degradation but within a small cadre also supporting deployed laboratories at other sites in SL, this led to significant issues of sustainability, and thus regular personnel were augmented by both the Army Reserve and the Royal Canadian Medical Service (RCMS).

Specimen transport

The safe movement of specimens that were potentially infected with EBOV was critical. The development of a triple package system with multiple decontamination steps provided a safe, although laborious, system of movement from the Red Zone to the clinical laboratory. Working in a two person team, the phlebotomist would fill a pre-labelled vacutainer blood collection tube in the normal way and then place it into an open 50ml Falcon tube held by the second team member who then applied and secured the lid. The exterior of the tube was sprayed with 0.5% chlorine and placed into a plastic bag. A request form with patient details and requested assays was placed in a separate plastic bag and both bags placed into a bucket of 0.5% chlorine, on which a lid was secured and the surface then decontaminated with 0.5% chlorine. This bucket was taken by one of the clinical team to a controlled interface between the Red Zone and exterior. Samples were passed over a 'dirty/clean' line and submerged in another bucket containing 0.5% chlorine and left to soak for 10 minutes. After moving to the laboratory, the plastic bag containing the specimen was flooded and left for 10 minutes to ensure complete surface decontamination. The BMS then matched the samples to the request form and moved the clean Falcon tubes, containing the samples, to the isolator via the pass box. Using large rubber gauntlets reaching into the isolator the samples could be removed from Falcon tube to start the analysis process.

Transfer of results

To prevent the potential transmission of EBOV, no paperwork left the laboratory. All results were scanned using a tablet within the facility and then electronically transferred to another tablet outside of the laboratory to the laboratory manager for manual input into the Laboratory Information Management System (LIMS) and hardcopy print off for inclusion in the patient's notes in the ward office.

Laboratory activity

In terms of routine activity, the deployed laboratory processed almost 3500 samples and issued nearly 200 units of blood components throughout the deployment (Table 2). The laboratory capability proved of crucial importance in supporting the clinicians in managing patients with both confirmed EVD and those with non-EVD diagnoses [8,9]. In addition, the BMS were involved throughout the deployment in research projects that required laboratory analysis and input, including validation of the BioFire Filmarray EBOV PCR platform [10] and contributing to the development of protocols for EBOV whole genome sequencing using a MinION device (Oxford Nanopore) [11].

Challenges and solutions

Whilst this unique clinical laboratory achieved its overall mission, there were many challenges which needed to be addressed to maintain the critical support capability, particularly those pertaining to the isolators, sample analysers and manning.

The initial isolator deployed had flexible pass boxes with zips. Within a few days several holes appeared in the gauntlets and isolator cuffs and a tear formed between the internal partition of the isolator and pass box. Although there was minimal risk of exposure to EBOV, due to the positive pressure system, the isolator was not suitable for on-going

Table 2. Summary of the laboratory activity at the Kerrytown EVDTU, Nov 2014-June 2015.

	Nov-14	Dec-14	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	TOTAL
FBC	41	326	235	207	149	81	89	48	1176
Amlyte	43	267	245	189	142	67	87	47	1087
Metlac	39	127	62	44	53	15	4	10	354
Coag	45	97	67	47	30	9	8	16	319
Malaria	12	3	33	19	16	73	7	4	167
HIV	7	13	21	8	17	0	1	4	71
Dengue	3	4	3	5	9	7	1	6	38
Blood Culture	15	27	19	14	11	9	5	5	105
D-Dimer	8	7	0	0	0	0	0	3	18
GI filmarray	11	3	15	18	10	7	8	7	79
Respfilmarray	0	0	6	3	3	1	0	0	13
Requests	224	874	731	592	440	269	210	152	**3492**
Transfusion									
RCC	8	3	0	3	6	0	0	0	20
FFP	43	54	13	20	2	0	0	0	132
Cryo	4	11	1	0	1	0	0	0	17
Platelets	8	10	3	0	0	0	0	0	21
Total Units	63	78	17	23	9	0	0	0	**190**

use and laboratory capability was restricted for 10 days whilst a second, identical isolator, was deployed from the UK and commissioned. Limited analysis using POCT continued in the Red Zone during this time. Despite the use of extreme care whilst moving samples into the second isolator, similar issues arose with tears and holes starting to appear within 14 days and this isolator was also decommissioned. Following further discussions with the manufacturers, PHE and other experts it was felt that the decontamination routine using 0.5% chlorine was likely degrading the flexible film which was contributing to the rapid failure of the units, however more significantly it was agreed that the pass boxes with zip connectors were simply not fit for purpose in a high throughput environment. A third isolator was deployed and commissioned which was still flexible film but with solid pass boxes and this, with a change of decontamination procedures throughout the military/PHE facility driven by corrosive effect on analysers of chlorine, using alcohol and latterly mild detergent provided a suitable, effective and reliable isolation system. The decontamination and cleaning regimes using chlorine also caused significant corrosion of analysers and led to failure of parts and one analyser during the operation. This was again improved by adapted decontamination procedures.

Undertaking specimen analysis using analysers inside the isolator was challenging due to the manual dexterity required whilst wearing four layers of gloves. Although the analysers were largely robust there were occasions where maintenance or repairs where required. If this could not be resolved within isolation then the analyser, which could not be decontaminated and repaired, would be safely removed and destroyed. All laboratory analysers employed had a recommended operating temperature range of 16-30^{O}C. However, the ambient temperature in Sierra Leone regularly exceeded the upper temperature limit and therefore the laboratory environment required air conditioning to ensure correct function. The air conditioning units supplied were insufficient to cope with the high temperatures in Sierra Leone and the presence of the analysers inside the isolator compounded this and occasionally led to overheating of the equipment causing a temporary loss of capability.

Finally, with the requirement to work in pairs at all times the reduction in numbers of BMS from five to three in the latter stages of the deployment resulted in difficulties in sustaining the operation of the laboratory capability. Future medically focussed deployments such as this mission to support the Ebola outbreak should consider the advice and recommendations of subject matter experts who have the expertise to ensure appropriate manning in order to maintain both the optimal function of the asset and also preserve the wellbeing of the deployed BMS.

Conclusions

CD Path successfully deployed a unique laboratory capability to Sierra Leone during the recent EVD outbreak, a capability unrivalled in its provision of support to the clinical teams. The delivery of haematology, biochemistry and coagulation and microbiology diagnostic tests was critical to the high standard of care delivered to patients with EVD and also to the management of those with febrile illness due to other aetiologies. The laboratory-generated information also supported a number of research projects and enabled greater clinical understanding of the pathogenesis of EVD. Reach back to UK experts for a variety of clinical, equipment and logistic issues was critical to this deployment and is likely to always be so in contingent operations. With recognition of the lessons learned from this deployment, Defence is ideally suited to deploy a similar capability to future operations where a Hazard Group 3 or 4 pathogen is suspected.

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