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Characterizing Post Ebola Syndrome: initial observations and future research agenda

Journal:	*Emerging Infectious Diseases*
Manuscript ID	EID-15-1302.R1
Manuscript Type:	Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Scott, Janet; University of Liverpool, Institute of Translational MEdicine; Janet Scott, Sesay, Foday; 34th Regimental Military Hospital, Wilberforce Barracks, Freetown, Sierra Leone, Massoquoi, Thomas; 34th Regimental Military Hospital, Wilberforce Barracks, Freetown, Sierra Leone, Idriss, Baimba; 34th Regimental Military Hospital, Wilberforce Barracks, Freetown, Sierra Leone, Sahr, Foday; 34th Regimental Military Hospital, Wilberforce Barracks, Freetown, Sierra Leone, Semple, Malcolm; University of Liverpool,
Keywords:	Post Ebola Syndrome, Sequelae, Ebola

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Additional notes or statements:

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21st October 2015

Dear Dr. Drotman,

Re: Characterising Post Ebola Syndrome: initial observations and future research agenda

Thank you for sending the kind, helpful and detailed comments of the referees for this manuscript. I would appreciate when appropriate, if you could forward our thanks for their time please. The manuscript describes Post Ebola Syndrome (PES) in a complete unselected cohort of survivors of Ebola Virus Disease (Zaire) discharged from a single Ebola Treatment Unit. Thus it is to ascertain the proportion of survivors suffering from each symptom facilitating health care planning and future research.

Please find attached a revised manuscript having responded to reviewers comment. The details are given below:

I hope it is now acceptable for publication.
.

Yours sincerely,

Dr. Janet Scott

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Changes made:

Note from the letter

Claims of primacy have been removed.

Figures to be uploaded in 300DPI. I note the instructions to authors requests 600 dpi – so this is what has been uploaded. 300dpi is possible, please do get back to me if this is preferred.

Specific Reviewers comments:

Regarding the short period of follow up the following has been added to the discussion: "Some complications occur weeks or months after the acute onset, so some symptoms may be underestimated in this cohort[2, 5]."

Regarding the request to revise the time to follow up based on the second negative blood test: records of the time of the negative blood tests are not available in all cases, however patients tended to wait a weeks until their physical health and social situation were suitable for them to be discharged. The abstract has therefore been revised to 'within 3 weeks of negative PCR' and this point made in more detail in the body of the text.

Regarding a control group: Past medical histories were collected from these patients but were not extracted for analysis. In general whilst there is some musculoskeletal pain and issues with visual acuity patients were able to distinguish between what occurred post Ebola and what was prior. Pre-existing conditions have not been included in the 'problem lists'. We have now established a more comprehensive data base which should document these patients, over the months that have now past, and indeed the other 250 patients who have now also registered with the clinic. So this is an issue that should be better addressed in follow up data.

Regarding preadmission CT values: These are not readily available although we are making efforts to collate them for future reference. The laboratories worked on a rota system so they were processed and assayed on different days, in different laboratories and on different platforms. The laboratories included Godrich, (South African Team), Public Health England, Port Locco and Kerrytown and the Chinese CDC. Consequently a groupwise comparison would likely lack validity and anyway in our opinion add little information to this survey of initial sequelae.

Regarding acknowledging that the convalescent whole blood was not powered to study its effect on PES: the following has been added to reflect that this is not a prospective study, so can no be claimed to be designed to detect a difference in treatment outcomes:

"23 of the survivors received CWB and 21 did not. There was no difference in age distribution of those transfused and those not transfused (p=0.8). There was no difference in the frequencies of symptoms between patients who received CWB and those who did not (p=0.5). This primary report on post-Ebola symptoms is not designed to consider the question of efficacy or toxicity of CWB.

The documentation of the patient who died has been extended.

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All minor changes in the attachment have been acted on including:

The section describing the ETU at MH34 has been shortened the section on data collection expanded.

Point 10. The point is well taken that this is by no means meant as a secondary outcome of the compassionate use trial of convalescent whole blood, but rather as justification of our using both patients who did and did not receive it. This section has been modified to:
"Symptoms do not appear to have been affected by use of CWB in the management of acute EVD. This finding should be interpreted with caution, as this report is not a prospective study and not designed to consider impact of CWB on PES.."

Reviewer 1. (From the email)

Line 96: Regarding time from second negative PCR to discharge. This information is not available in this data extraction, which was a simple documentation of problem lists by the first formal health check. Patients often come in informally in an ad hoc basis. Now the survivors clinic and data collection are more formalised, future follow ups can be more precise. Discharge criteria has been moved to this point.

Details of the age group and gender characteristics of musculoskeletal pain and ocular pain have been removed. There seems to be less children reporting headache than adults. Whilst the numbers would, in my opinion, be too small to draw any conclusions. we have left the numbers in the paper to they can be available for other studies in the future.

This paper does not correlated the acute Ebola history post Ebola syndrome with illness severity and nor does it claim to – these patients along with about 250 others are being recruited to track their progress over the subsequent months and years where possible also collect data about their time as acute inpatients. Even for clinical trial patients however this has proved to be a much harder ask than it might seem and remains a work in progress.

The reviewer thought that MH34 catered only to health care workers. This was not the case. MH34 although staffed by the military hospital mostly admits civilian from the Western Urban Area Freetown. I wonder if possibly the reviewer is thinking about the Kerrytown UK MoD military run unit that did only admit expatriate staff or health care workers.

Thank you again for the comments, I hope the manuscript is now suitable for publication.

Characterising Post Ebola Syndrome: initial observations and future research agenda

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Funding.

JTS is supported by the Wellcome Trust.

MGS is supported by the UK NIHR Health Protection Research Unit in Emerging and Zoonotic Infections.

Summary

Thousands have survived Ebola virus disease (EVD). Almost all survivors describe symptoms that persist or develop after discharge. We describe the symptoms in a complete unselected cohort of patients discharged from a single Ebola treatment unit (ETU). A cross-sectional survey of the symptoms of all survivors from the ETU at 34th Regimental Military Hospital, Freetown, Sierra Leone (MH34) was conducted after discharge at their initial follow-up appointment within three weeks of their second negative PCR. Between opening on 1st December 2014, and 30th March 2015 the MH34 ETU treated 84 people with PCR confirmed Ebola. 44 survived (21 males, 23 females, age 8 to 70 years old. Survivors complain of musculoskeletal pain (70%), headache (48%) and ocular problems (14%). This complete survivor cohort from a single ETU allows an analysis of the proportion of symptoms of Post Ebola Syndrome to be made.

One Line summary:

A cross sectional survey of Post Ebola Syndrome within three weeks of second negative PCR from a complete unselected cohort indicated Ebola survivors suffer from a range of conditions which are dominated by musculoskeletal pain (70%), headache (48%) and ocular problems (14%).

Biography of First Author.

Dr Janet Scott is a Clinical Lecturer in Pharmacology and Infectious Diseases at the Institute of Translational Medicine, University of Liverpool.

Thousands of people have now survived Ebola Virus Disease (EVD). In the fight to control the current Ebola-Zaire outbreak, attention has focused on containing the spread of infection and improving survival of the sick. It is estimated that there are between 4051 and 5115 survivors in Sierra Leone (8704 confirmed cases, 3589 confirmed deaths, 4051 confirmed discharges [1]).

Survivors complain of a range of sequelae loosely described as 'Post Ebola Syndrome' (PES). Follow-up clinics were not always planned as part of the emergency response. However, survivors from the ETU at the 34th Regimental Military Hospital, Wilberforce Barracks, Freetown, Sierra Leone (MH34) were all followed up in an outpatient clinic within two weeks of discharge. Although resources for the care of survivors, including basic equipment such as adequate stethoscopes was scarce at this time, each survivor was seen by a physician who made contemporaneous structured notes. This affords an opportunity to document PES in these first weeks.

It is not clear what proportion of Ebola survivors are suffering sequelae. Little is known about 'Post Ebola Syndrome', or even if it is an entity distinct from an appropriate response to the traumatic events. Abdominal pains, loss of vision, loss of hearing, impotence, bleeding, psychological problems, and general weakness were listed qualitatively as symptoms of PES, following the Ebola-Sudan outbreak (Uganda 2000)[2]. Arthralgia and ocular diseases, were noted in 19 survivors (selected according to availability) who were followed up after the Ebola-Zaire outbreak in Kikwit (1995) [3, 4] and in the same outbreak, arthralgia, myalgia, abdominal pain, extreme fatigue and anorexia were more common in Ebola survivors than in household contacts [5]. From the current outbreak, survivors reported arthralgia and "anorexia" (which in this context includes loss of appetite without weight loss) in a telephone

administered questionnaire in Guinea when asked some months after discharge[6]. None of these studies were an unselected cohort of survivors so interpretation of proportions was difficult. Other reports refer to anecdotes of pain, weakness, difficulty hearing and 'mental disturbances[7, 8]. These observations give some idea of what complaints might be expected. Describing the proportions needing care for the most common problems is important for planning the health care of the thousands of survivors. We report the symptoms described by all survivors from one Ebola treatment unit (ETU) in the initial weeks after discharge.

Methods.

The MH34 ETU is a facility that could care for up to 30 confirmed cases of EVD, plus 20 suspect cases. It opened on 1st December 2014 with 115 staff including 3 doctors. It catered for patients falling ill in Western Freetown and surrounds. The ETU admitted 355 patients, 84 positive patients and discharged 44 survivors between December and March 2015. The ETU at MH34 consists of a suspect and confirmed areas and a doffing area. The confirmed zone is a permanent building including several one to four bedded rooms with electric lighting and ceiling fans. Three hot meals per day are provided, generally rice with protein such as fish or chicken; each with two bags of water. The staff of this small ETU are all permanent Sierra Leonean health care workers.

Patients were treated for EVD, with supportive care [9]. At the MH34 empirical antibiotics and artesunate, paracetamol, and 500ml intravenous Ringer's Lactate were administered on arrival. On-going treatment included: further boluses of intravenous fluid, antiemetic's and proton pump inhibitors; that were administered according to clinical need. Some patients participated in a compassionate use open non-randomised study of a single unit of convalescent whole blood (CWB), results of which are pending.

Discharge criteria were: two consecutive negative EBOV PCR tests taken on separate days; medically fit in the opinion of their physician; and when adequate social provision had been made, including when their house and household members being released from quarantine. Records of the dates of individual negative PCRs are unfortunately not available, however patients tended to stay and convalesce in the ETU for about a week after their negative results. During the convalescent period many patients ate more than one serving of each meal, three times a day. Although they were not routinely weighed most patients visibly gained weight.

All survivors were issued with a survivor's certificate on leaving the ETU and invited to a follow-up appointment within two weeks of discharge. Some were seen prior to this appointment due to clinical need.

Contact with survivors was maintained by mobile phone. Confirmation of identification has not proved problematic, as the patients and health care workers had come to know each other well. Appointments are made by mobile phone and unscheduled visits by patients to the hospital. All survivors attended their follow-up. Patients were examined by one of three experienced physicians.

A follow-up appointment was established as a standard of care in this ETU from the outset, at the height of the epidemic. Handwritten clinical notes were taken documenting presenting complaints, symptoms and signs. These notes were subsequently used to develop appropriate pre-printed clinical documentation. Age, sex, presenting complaints, and history of transfusion with CWB were noted for each patient. Pre-existing conditions were rare in this cohort of patients, and not included in this data extraction. At that time facilities and equipment for survivors was very limited. For example all stethoscopes had been incinerated; blood pressure cuffs, ophthalmoscopes, and specialist opinions were not available.

Data Analysis.

Confidence intervals and hypothesis testing of binomial outcomes (binomial frequency test) were analysed using Stata v9 (StataCorp LP, Texas USA) [10]. Graphics were produced using Stata v9 and R v3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between opening on 1st December 2014, and 30th March 2015 the MH34 ETU had treated 84 people with PCR confirmed EVD. 44 survived (21 male, 23 female, age range 8 to 70 years old median age 35 years (IQR 20-37yr), age not documented in 1 case)) (Figure 1). 23 of the survivors received CWB and 21 did not. There was no difference in age distribution of those transfused and those not transfused (p=0.8). There was no difference in the frequencies of symptoms between patients who received CWB and those who did not (p=0.5). This primary report on post-Ebola symptoms is not designed to consider the question of efficacy or toxicity of CWB.

At the time of this data extraction each patient had attended a maximum of two appointments. All survivors presented with at least one post Ebola complaint, a median of 2 complaints and a maximum of 5. 117 separate presenting complaints were reported. 70% of patients suffered from musculoskeletal pain (31/44 CI 55-83%), 48% of patients (21/44, CI 32-63%) suffered from headaches and 14% of patients (6/44, CI 5-27%) suffered from ocular problems.

One patient died following gradually deteriorating respiratory symptoms and a left sided pleural effusion. He was a 25 year old man, diagnosed with Ebola on 26th January, and treated with supportive care and 1 unit of CWB. He received his first negative PCR result on 8th February and his confirmatory negative test on 11th February, and was discharged home. At his 14 day follow-up he was noted to have weight loss, cough and dyspnoea on exertion. He was admitted on his second outpatient appointment to the general medical ward on 3rd March 2015 with a left sided pleural effusion. A pleural tap was attempted, but yielded only a small quantity of blood stained fluid that was insufficient for analysis. He died after a short inpatient stay on 8th March 2015, a month after his recovery from acute EVD. Adhering to safe-burial policy, a post-mortem examination was not performed. His diagnosis remains

unclear but a post-viral effusion is possible with tuberculosis pleural effusion being a differential diagnosis.

Musculoskeletal Pain.

70% of patients (31/44, CI 55-83%) suffered from musculoskeletal pain. In our experience and in the local context the distinction between myalgia and arthralgia can be a doctor dependent label. In these circumstances we chose to merge these complaints. However for the purposes of comparisons with other studies, 12/44 (27% CI: 15-42%) had problems labelled as 'arthralgia' , 15/44 (27% CI: 20-50%) had 'myalgia' and 4/44 (9% CI 3-22%) had both. Individual problems are listed in Table 1. There were no statistically significant differences between the proportion of males and females; nor children (<18 years) and adults suffering from musculoskeletal pain.

Musculoskeletal pain is variously described by patients as problems with walking or moving, or pain specific to one area, such as knees, thighs or back, or a generalised musculoskeletal pain (21-52%.) The picture is more often one of a general pain rather than a specific joint or area. This is reflected in the recorded symptoms, the most common of which are unspecified joint pain (36%, 14/39 CI 21-52% recorded) and generalised body pain (21%: 8/39 CI 9-36%) (Table 1).

On examination there is no indication of inflamed joints or joint effusions, such as might be expected in a reactive picture and a full range of movement is retained. A description of functional disability suggests that the range is from mild to moderate. For example, one male patient in his twenties, continues to play football, but now takes paracetamol (acetaminophen) to facilitate this, whereas another female patient in her forties requires assistance to step into a bath and is no longer able to continue normal household work. She was able to walk

unaided into clinic, but needed assistance to step up into the clinic room and to sit and stand. Most musculoskeletal symptoms are relieved by simple analgesia.

Headache

48% of patients (21/44, CI 32-63%) suffered from headaches. Two (of Twenty-one) (10%, CI 1-30%) of these were children, both female and aged 8 and 11 years. There was no statistically significant difference between the proportion of males and females suffering from headaches (Chi^2, p=1). Headache is generally described as affecting the full head, with no diurnal pattern and being constant. Ocular symptoms may coincide, but there are no visual phenomena reported such as might be found in migraine. These symptoms could represent on-going tension headaches, or may be a result of underlying undiagnosed changes in vision.

Ocular Symptoms

14% of patients (6/44, CI 5-27%) suffered from ocular problems. Symptoms included eye pain, clear eye discharge, red eyes and blurred vision (Table 2). These symptoms appeared within 2 weeks of discharge and were not present at discharge from the ETU or before. At this time the facility for ophthalmology review was not available. Eye discharge was treated with topical chloramphenicol. Ophthalmology services for survivors are currently under development.

Combinations of Musculoskeletal Pain, Headache and Ocular problems.

There is a substantial overlap between the presentation of musculoskeletal pain and headache. 18 patients complained of both. This is 58% (18/31, CI 40-75%) of patients with musculoskeletal pain and 86% (18/21, CI 64-97%) of patients with headache. Two patients had both ocular problems and musculoskeletal pain. This was 6% (2/31, CI 1-21%) of patients with musculoskeletal pain and 33% (2/6, CI 4-78%) of patients with ocular

problems. Two patients had both headache and ocular problems (2/21, 6%, CI 1-30% of patients with headache). One patient had all three complaints (1/31, 3% 1-17% of patients with musculoskeletal pain, 1/21, 5%, CI 0-24% of patients with headache and 15% 1/6, CI 0-64% of patients with ocular problems). These relationships are graphically described in a scaled Venn diagram (Figure 2).

Other Symptoms

60% of patients (26/44, CI 43-74%) suffered from other symptoms. 11% (5/44, CI 4-25) complained of cough, 9% (4/44, CI 3-22%) complained of abdominal pain, 9% of chest pain, and 9% of itching. 7% (3/44 CI 1-19%) complained of insomnia, 7% fever and 7% loss of appetite, 5% (2/44 1-15%) complained of laboured speech, 5% epigastric pain and 5% rash, and the remaining symptoms were reported by one person each (2% CI 0-12%). These other symptoms were: weight loss, hiccups, increased appetite, chest pain, sneezing, diarrhoea, vomiting, left sided weakness with facial nerve palsy, breathlessness, rash, dry flaky skin, earache, fever blister/cold sore, left scrotal swelling, nasal congestion and tremors.

Discussion.

This survey documents symptoms of Ebola survivors in the initial three weeks post negative EBOV PCR and two weeks after discharge from the treatment centre. The dominant clinical features exhibited by this survivor cohort were musculoskeletal pain, headache, and ocular problems. Symptoms did not differ with gender or age in this cohort. Symptoms do not appear to have been affected by use of CWB in the management of acute EVD. This finding should be interpreted with caution, as this report is not a prospective study and not designed to consider impact of CWB on PES. Whether this collection of signs and symptoms experienced after acute EVD constitute a separate 'syndrome' or not may be semantic argument. The experience of patients in the weeks after Ebola, although varied, has common features so we propose that the term Post Ebola Syndrome (PES) is useful to describe these phenomena.

Our findings are consistent with some aspects of previous reports [2, 5] but vary from others. For example, the prevalence of extreme fatigue and anorexia reported in Kikwit and Guinea [5, 6] has not been dominant in this cohort. This may be due to the period of inpatient convalescence that the survivors had at MH34 with substantial nutritional support.

We hypothesise that the pathogenesis of pain, particularly the muscle pain is a sequelae of widespread myositis or rhabdomyolysis during acute EVD. This would be consistent with laboratory data reporting raised transaminases and disseminated intravascular coagulation from a previous outbreak of Sudan EVD [11]. Future research would benefit from a comparison of a survivors cohort with a matched group who had not had Ebola and, if this pain is more common in Ebola survivors (as was found in Kikwit [5]), further elucidation of its aetiology would be useful in determining treatment strategies.

PES includes musculoskeletal pain, headache and ocular problems but is not restricted to these areas. Some complications occur weeks or months after the acute onset, so some symptoms may be underestimated in this cohort[2, 5]. Since this data was extracted clinical facilities and documentation has improved so future information is likely to be more detailed in terms of specific diagnosis, and scope. This is particularly true in the areas of psycho-social health and ophthalmology. Previous outbreaks have reported psychosocial problems [2] although it is not included in all reports [5]. Psycho-social problems are also evident in our patient group, although not captured in the documentation to date. Improved collaboration with the hospital's mental health team should improve both the care and documentation in the future. Anecdotal evidence from the survivors' clinic suggests that more subtle neurological problems such as specific nerve palsies may feature more heavily in a follow-up study.

We would expect that the criteria and definition of PES will continue to develop and that the patients continue to present with fresh challenges. During the height of the epidemic, when these consultations took place, resources, and equipment for assessing survivors was very limited. This survey documents symptoms only in the first two weeks of discharge. Subsequent follow-up may be more detailed and benefit from increased resources, and symptoms continue to develop with time. Indeed the virus can cross the blood brain barrier during the acute illness [12] , and persist in some compartments for some months[13] . PES may continue to present new challenges. Areas for development include: comparison of symptoms to community controls, psycho-social problems, the aetiology of ocular problems and musculoskeletal pain, and longitudinal description of the clinical picture.

Musculoskeletal pain is a common complaint in the general population in Sierra Leone so a community controlled comparison will be important. In survivors of the Kikwit Ebola Zaire outbreak in 1995, Rowe *et al.* reported that their key features: Arthralgia, myalgia, abdominal

pain, fatigue and anorexia were more common in convalescents than household contacts, whereas fever, headache, diarrhoea, dyspnea, hiccups, haemorrhage were the same in survivors and the control group[5]. A topic for future research is the longitudinal course of recovery. Wendo et al [2] report that one year after the Ebola Zaire outbreak in Uganda, 25% of patients were still reporting to clinic. We can expect therefore some patients to have long term clinical needs. The epidemic is waning but the burden of disease it caused will remain for some time to come.

2693 words

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Acknowledgements.

Funding: JTS is supported by the Wellcome Trust. MGS is supported by UK NIHR Health Protection Research Unit in Emerging and Zoonotic Infections. The authors have been

328 awarded a grant from the Wellcome Trust to support further research into the sequelae of
329 Ebola Virus Disease.
330 **Statistics**: Stata 9, R v3.1.1, R package [S Urbanek; simon.urbanek@r-project.org]
331 & Venneuler Package [L Wilkinson; leland.wilkinson@gmail.com]
332
333

Figure 1. Age distribution of patients presenting to the 34th Military Hospital Ebola Survivor's Clinic.

Note to editors: The image of the histogram has been uploaded separately as a 600dpi tif file. We would envisage this being presented in conjunction with this small table as a single figure. I have left this separate according to the instructions to authors to maximise editability.

	Male	Female	Total
N	21	22	44
Median	30	25	25
IQR	22-37	20-34	20-37
Range	10-52	8-70	8-70

Table 1: The frequencies of musculoskeletal symptoms. Some individuals complained of more than one area of pain. There was no statistically significant difference between the proportion of males and females suffering from musculoskeletal pain. (Chi^2, p=0.7).

	Sex		
Area of Pain	**Male**	**Female**	**Total**
Joint Unspecified	5	9	14
Knee Unspecified	2	0	2
Right Knee Joint	0	1	1
Shoulder Joint	1	1	2
Generalised Body	4	4	8
Upper Back Pain	1	3	4
Musculo-skeletal Unspecified	2	0	2
Left Thigh	1	1	2
Lower Limb	0	1	1
Right Thigh	1	0	1
Gluteal Muscle	1	0	1

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346 **Table 2:** Ocular Symptoms: described by patients. Two patients were children and four were
347 adults**.**
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Age	Sex	Symptom
8	F	eye pain
14	F	clear eye discharge
20	F	clear eye discharge
28	F	red eyes and blurred vision on the left
29	F	red eyes
46	M	blurred vision

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Table 3: Number of patients presenting with of other presenting complaints

Presenting Complaint	N	%	Confidence Intervals (%)
Cough	5	11	4-25
Abdominal pain	4	9	3-22
Chest pain	4	9	3-22
Itching	4	9	3-22
Insomnia	3	7	1-19
Fever	3	7	1-19
Loss of appetite	3	7	1-19
Laboured speech	2	5	1-15
Epigastric pain	2	5	1-15
Rash	2	5	1-5
17 other symptoms*	1	2	0-12

*Weight Loss, Hiccups, increased appetite, chest pain, sneezing, diarrhoea, vomiting, left sided weakness with facial nerve palsy, breathlessness, rash, dry flaky skin, earache, fever blister/cold sore, left scrotal swelling, nasal congestion, tremors

359 **Figure 2.**

360 A scale Venn diagram illustrating the overlap between the three main symptom groups.

361 Seven patients did not have any other the three main symptom groups.

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Characterising Post Ebola Syndrome: initial observations and future research agenda

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Funding.

JTS is supported by the Wellcome Trust.

MGS is supported by the UK NIHR Health Protection Research Unit in Emerging and Zoonotic Infections.

Summary

Thousands have survived Ebola virus disease (EVD). Almost all survivors describe symptoms that persist or develop after discharge. We describe the symptoms in a complete unselected cohort of patients discharged from a single Ebola treatment unit (ETU). A cross-sectional survey of the symptoms of all survivors from the ETU at 34th Regimental Military Hospital, Freetown, Sierra Leone (MH34) was conducted after discharge at their initial follow-up appointment within three weeks of their second negative PCR. Between opening on 1st December 2014, and 30th March 2015 the MH34 ETU treated 84 people with PCR confirmed Ebola. 44 survived (21 males, 23 females, age 8 to 70 years old. Survivors complain of musculoskeletal pain (70%), headache (48%) and ocular problems (14%). This complete survivor cohort from a single ETU allows an analysis of the proportion of symptoms of Post Ebola Syndrome to be made.

One Line summary:

A cross sectional survey of Post Ebola Syndrome within three weeks of second negative PCR from a complete unselected cohort indicated Ebola survivors suffer from a range of conditions which are dominated by musculoskeletal pain (70%), headache (48%) and ocular problems (14%).

Biography of First Author.

Dr Janet Scott is a Clinical Lecturer in Pharmacology and Infectious Diseases at the Institute of Translational Medicine, University of Liverpool.

Thousands of people have now survived Ebola Virus Disease (EVD). In the fight to control the current Ebola-Zaire outbreak, attention has focused on containing the spread of infection and improving survival of the sick. It is estimated that there are between 4051 and 5115 survivors in Sierra Leone (8704 confirmed cases, 3589 confirmed deaths, 4051 confirmed discharges [1]).

Survivors complain of a range of sequelae loosely described as 'Post Ebola Syndrome' (PES). Follow-up clinics were not always planned as part of the emergency response. However, survivors from the ETU at the 34th Regimental Military Hospital, Wilberforce Barracks, Freetown, Sierra Leone (MH34) were all followed up in an outpatient clinic within two weeks of discharge. Although resources for the care of survivors, including basic equipment such as adequate stethoscopes was scarce at this time, each survivor was seen by a physician who made contemporaneous structured notes. This affords an opportunity to document PES in these first weeks.

It is not clear what proportion of Ebola survivors are suffering sequelae. Little is known about 'Post Ebola Syndrome', or even if it is an entity distinct from an appropriate response to the traumatic events. Abdominal pains, loss of vision, loss of hearing, impotence, bleeding, psychological problems, and general weakness were listed qualitatively as symptoms of PES, following the Ebola-Sudan outbreak (Uganda 2000)[2]. Arthralgia and ocular diseases, were noted in 19 survivors (selected according to availability) who were followed up after the Ebola-Zaire outbreak in Kikwit (1995) [3, 4] and in the same outbreak, arthralgia, myalgia, abdominal pain, extreme fatigue and anorexia were more common in Ebola survivors than in household contacts [5]. From the current outbreak, survivors reported arthralgia and "anorexia" (which in this context includes loss of appetite without weight loss) in a telephone

administered questionnaire in Guinea when asked some months after discharge[6]. None of these studies were an unselected cohort of survivors so interpretation of proportions was difficult. Other reports refer to anecdotes of pain, weakness, difficulty hearing and 'mental disturbances[7, 8]. These observations give some idea of what complaints might be expected. Describing the proportions needing care for the most common problems is important for planning the health care of the thousands of survivors. We report the symptoms described by all survivors from one Ebola treatment unit (ETU) in the initial weeks after discharge.

Methods.

The MH34 ETU is a facility that could care for up to 30 confirmed cases of EVD, plus 20 suspect cases. It opened on 1st December 2014 with 115 staff including 3 doctors. It catered for patients falling ill in Western Freetown and surrounds. The ETU admitted 355 patients, 84 positive patients and discharged 44 survivors between December and March 2015. The ETU at MH34 consists of a suspect and confirmed areas and a doffing area. The confirmed zone is a permanent building including several one to four bedded rooms with electric lighting and ceiling fans. Three hot meals per day are provided, generally rice with protein such as fish or chicken; each with two bags of water. The staff of this small ETU are all permanent Sierra Leonean health care workers.

Patients were treated for EVD, with supportive care [9]. At the MH34 empirical antibiotics and artesunate, paracetamol, and 500ml intravenous Ringer's Lactate were administered on arrival. On-going treatment included: further boluses of intravenous fluid, antiemetic's and proton pump inhibitors; that were administered according to clinical need. Some patients participated in a compassionate use open non-randomised study of a single unit of convalescent whole blood (CWB), results of which are pending.

Discharge criteria were: two consecutive negative EBOV PCR tests taken on separate days; medically fit in the opinion of their physician; and when adequate social provision had been made, including when their house and household members being released from quarantine. Records of the dates of individual negative PCRs are unfortunately not available, however patients tended to stay and convalesce in the ETU for about a week after their negative results. During the convalescent period many patients ate more than one serving of each meal, three times a day. Although they were not routinely weighed most patients visibly gained weight.

All survivors were issued with a survivor's certificate on leaving the ETU and invited to a follow-up appointment within two weeks of discharge. Some were seen prior to this appointment due to clinical need.

Contact with survivors was maintained by mobile phone. Confirmation of identification has not proved problematic, as the patients and health care workers had come to know each other well. Appointments are made by mobile phone and unscheduled visits by patients to the hospital. All survivors attended their follow-up. Patients were examined by one of three experienced physicians.

A follow-up appointment was established as a standard of care in this ETU from the outset, at the height of the epidemic. Handwritten clinical notes were taken documenting presenting complaints, symptoms and signs. These notes were subsequently used to develop appropriate pre-printed clinical documentation. Age, sex, presenting complaints, and history of transfusion with CWB were noted for each patient. Pre-existing conditions were rare in this cohort of patients, and not included in this data extraction. At that time facilities and equipment for survivors was very limited. For example all stethoscopes had been incinerated; blood pressure cuffs, ophthalmoscopes, and specialist opinions were not available.

Data Analysis.

Confidence intervals and hypothesis testing of binomial outcomes (binomial frequency test) were analysed using Stata v9 (StataCorp LP, Texas USA) [10]. Graphics were produced using Stata v9 and R v3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between opening on 1st December 2014, and 30th March 2015 the MH34 ETU had treated 84 people with PCR confirmed EVD. 44 survived (21 male, 23 female, age range 8 to 70 years old median age 35 years (IQR 20-37yr), age not documented in 1 case)) (Figure 1). 23 of the survivors received CWB and 21 did not. There was no difference in age distribution of those transfused and those not transfused (p=0.8). There was no difference in the frequencies of symptoms between patients who received CWB and those who did not (p=0.5). This primary report on post-Ebola symptoms is not designed to consider the question of efficacy or toxicity of CWB.

At the time of this data extraction each patient had attended a maximum of two appointments. All survivors presented with at least one post Ebola complaint, a median of 2 complaints and a maximum of 5. 117 separate presenting complaints were reported. 70% of patients suffered from musculoskeletal pain (31/44 CI 55-83%), 48% of patients (21/44, CI 32-63%) suffered from headaches and 14% of patients (6/44, CI 5-27%) suffered from ocular problems.

One patient died following gradually deteriorating respiratory symptoms and a left sided pleural effusion. He was a 25 year old man, diagnosed with Ebola on 26th January, and treated with supportive care and 1 unit of CWB. He received his first negative PCR result on 8th February and his confirmatory negative test on 11th February, and was discharged home. At his 14 day follow-up he was noted to have weight loss, cough and dyspnoea on exertion. He was admitted on his second outpatient appointment to the general medical ward on 3rd March 2015 with a left sided pleural effusion. A pleural tap was attempted, but yielded only a small quantity of blood stained fluid that was insufficient for analysis. He died after a short inpatient stay on 8th March 2015, a month after his recovery from acute EVD. Adhering to safe-burial policy, a post-mortem examination was not performed. His diagnosis remains

unclear but a post-viral effusion is possible with tuberculosis pleural effusion being a differential diagnosis.

Musculoskeletal Pain.

70% of patients (31/44, CI 55-83%) suffered from musculoskeletal pain. In our experience and in the local context the distinction between myalgia and arthralgia can be a doctor dependent label. In these circumstances we chose to merge these complaints. However for the purposes of comparisons with other studies, 12/44 (27% CI: 15-42%) had problems labelled as 'arthralgia' , 15/44 (27% CI: 20-50%) had 'myalgia' and 4/44 (9% CI 3-22%) had both. Individual problems are listed in Table 1. There were no statistically significant differences between the proportion of males and females; nor children (<18 years) and adults suffering from musculoskeletal pain.

Musculoskeletal pain is variously described by patients as problems with walking or moving, or pain specific to one area, such as knees, thighs or back, or a generalised musculoskeletal pain (21-52%.) The picture is more often one of a general pain rather than a specific joint or area. This is reflected in the recorded symptoms, the most common of which are unspecified joint pain (36%, 14/39 CI 21-52% recorded) and generalised body pain (21%: 8/39 CI 9-36%) (Table 1).

On examination there is no indication of inflamed joints or joint effusions, such as might be expected in a reactive picture and a full range of movement is retained. A description of functional disability suggests that the range is from mild to moderate. For example, one male patient in his twenties, continues to play football, but now takes paracetamol (acetaminophen) to facilitate this, whereas another female patient in her forties requires assistance to step into a bath and is no longer able to continue normal household work. She was able to walk

unaided into clinic, but needed assistance to step up into the clinic room and to sit and stand. Most musculoskeletal symptoms are relieved by simple analgesia.

Headache

48% of patients (21/44, CI 32-63%) suffered from headaches. Two (of Twenty-one) (10%, CI 1-30%) of these were children, both female and aged 8 and 11 years. There was no statistically significant difference between the proportion of males and females suffering from headaches (Chi^2, p=1). Headache is generally described as affecting the full head, with no diurnal pattern and being constant. Ocular symptoms may coincide, but there are no visual phenomena reported such as might be found in migraine. These symptoms could represent on-going tension headaches, or may be a result of underlying undiagnosed changes in vision.

Ocular Symptoms

14% of patients (6/44, CI 5-27%) suffered from ocular problems. Symptoms included eye pain, clear eye discharge, red eyes and blurred vision (Table 2). These symptoms appeared within 2 weeks of discharge and were not present at discharge from the ETU or before. At this time the facility for ophthalmology review was not available. Eye discharge was treated with topical chloramphenicol. Ophthalmology services for survivors are currently under development.

Combinations of Musculoskeletal Pain, Headache and Ocular problems.

There is a substantial overlap between the presentation of musculoskeletal pain and headache. 18 patients complained of both. This is 58% (18/31, CI 40-75%) of patients with musculoskeletal pain and 86% (18/21, CI 64-97%) of patients with headache. Two patients had both ocular problems and musculoskeletal pain. This was 6% (2/31, CI 1-21%) of patients with musculoskeletal pain and 33% (2/6, CI 4-78%) of patients with ocular

problems. Two patients had both headache and ocular problems (2/21, 6%, CI 1-30% of patients with headache). One patient had all three complaints (1/31, 3% 1-17% of patients with musculoskeletal pain, 1/21, 5%, CI 0-24% of patients with headache and 15% 1/6, CI 0-64% of patients with ocular problems). These relationships are graphically described in a scaled Venn diagram (Figure 2).

Other Symptoms

60% of patients (26/44, CI 43-74%) suffered from other symptoms. 11% (5/44, CI 4-25) complained of cough, 9% (4/44, CI 3-22%) complained of abdominal pain, 9% of chest pain, and 9% of itching. 7% (3/44 CI 1-19%) complained of insomnia, 7% fever and 7% loss of appetite, 5% (2/44 1-15%) complained of laboured speech, 5% epigastric pain and 5% rash, and the remaining symptoms were reported by one person each (2% CI 0-12%). These other symptoms were: weight loss, hiccups, increased appetite, chest pain, sneezing, diarrhoea, vomiting, left sided weakness with facial nerve palsy, breathlessness, rash, dry flaky skin, earache, fever blister/cold sore, left scrotal swelling, nasal congestion and tremors.

Discussion.

This survey documents symptoms of Ebola survivors in the initial three weeks post negative EBOV PCR and two weeks after discharge from the treatment centre. The dominant clinical features exhibited by this survivor cohort were musculoskeletal pain, headache, and ocular problems. Symptoms did not differ with gender or age in this cohort. Symptoms do not appear to have been affected by use of CWB in the management of acute EVD. This finding should be interpreted with caution, as this report is not a prospective study and not designed to consider impact of CWB on PES. Whether this collection of signs and symptoms experienced after acute EVD constitute a separate 'syndrome' or not may be semantic argument. The experience of patients in the weeks after Ebola, although varied, has common features so we propose that the term Post Ebola Syndrome (PES) is useful to describe these phenomena.

Our findings are consistent with some aspects of previous reports [2, 5] but vary from others. For example, the prevalence of extreme fatigue and anorexia reported in Kikwit and Guinea [5, 6] has not been dominant in this cohort. This may be due to the period of inpatient convalescence that the survivors had at MH34 with substantial nutritional support.

We hypothesise that the pathogenesis of pain, particularly the muscle pain is a sequelae of widespread myositis or rhabdomyolysis during acute EVD. This would be consistent with laboratory data reporting raised transaminases and disseminated intravascular coagulation from a previous outbreak of Sudan EVD [11]. Future research would benefit from a comparison of a survivors cohort with a matched group who had not had Ebola and, if this pain is more common in Ebola survivors (as was found in Kikwit [5]), further elucidation of its aetiology would be useful in determining treatment strategies.

PES includes musculoskeletal pain, headache and ocular problems but is not restricted to these areas. Some complications occur weeks or months after the acute onset, so some symptoms may be underestimated in this cohort[2, 5]. Since this data was extracted clinical facilities and documentation has improved so future information is likely to be more detailed in terms of specific diagnosis, and scope. This is particularly true in the areas of psycho-social health and ophthalmology. Previous outbreaks have reported psychosocial problems [2] although it is not included in all reports [5]. Psycho-social problems are also evident in our patient group, although not captured in the documentation to date. Improved collaboration with the hospital's mental health team should improve both the care and documentation in the future. Anecdotal evidence from the survivors' clinic suggests that more subtle neurological problems such as specific nerve palsies may feature more heavily in a follow-up study.

We would expect that the criteria and definition of PES will continue to develop and that the patients continue to present with fresh challenges. During the height of the epidemic, when these consultations took place, resources, and equipment for assessing survivors was very limited. This survey documents symptoms only in the first two weeks of discharge. Subsequent follow-up may be more detailed and benefit from increased resources, and symptoms continue to develop with time. Indeed the virus can cross the blood brain barrier during the acute illness [12] , and persist in some compartments for some months[13] . PES may continue to present new challenges. Areas for development include: comparison of symptoms to community controls, psycho-social problems, the aetiology of ocular problems and musculoskeletal pain, and longitudinal description of the clinical picture.

Musculoskeletal pain is a common complaint in the general population in Sierra Leone (J Whitworth *pers comm*), so a community controlled comparison will be important. In survivors of the Kikwit Ebola Zaire outbreak in 1995, Rowe *et al.* reported that their key

features: Arthralgia, myalgia, abdominal pain, fatigue and anorexia were more common in convalescents than household contacts, whereas fever, headache, diarrhoea, dyspnea, hiccups, haemorrhage were the same in survivors and the control group[5]. A topic for future research is the longitudinal course of recovery. Wendo et al [2] report that one year after the Ebola Zaire outbreak in Uganda, 25% of patients were still reporting to clinic. We can expect therefore some patients to have long term clinical needs. The epidemic is waning but the burden of disease it caused will remain for some time to come.

2693 words

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Acknowledgements.

Funding: JTS is supported by the Wellcome Trust. MGS is supported by UK NIHR Health Protection Research Unit in Emerging and Zoonotic Infections. The authors have been

328 awarded a grant from the Wellcome Trust to support further research into the sequelae of
329 Ebola Virus Disease.
330 **Statistics**: Stata 9, R v3.1.1, R package [S Urbanek; simon.urbanek@r-project.org]
331 & Venneuler Package [L Wilkinson; leland.wilkinson@gmail.com]
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Figure 1. Age distribution of patients presenting to the 34th Military Hospital Ebola Survivor's Clinic.

Note to editors: The image of the histogram has been uploaded separately as a 600dpi tif file. We would envisage this being presented in conjunction with this small table as a single figure. I have left this separate according to the instructions to authors to maximise editability.

	Male	Female	Total
N	21	22	44
Median	30	25	25
IQR	22-37	20-34	20-37
Range	10-52	8-70	8-70

Table 1: The frequencies of musculoskeletal symptoms. Some individuals complained of more than one area of pain. There was no statistically significant difference between the proportion of males and females suffering from musculoskeletal pain. (Chi^2, p=0.7).

	Sex		
Area of Pain	**Male**	**Female**	**Total**
Joint Unspecified	5	9	14
Knee Unspecified	2	0	2
Right Knee Joint	0	1	1
Shoulder Joint	1	1	2
Generalised Body	4	4	8
Upper Back Pain	1	3	4
Musculo-skeletal Unspecified	2	0	2
Left Thigh	1	1	2
Lower Limb	0	1	1
Right Thigh	1	0	1
Gluteal Muscle	1	0	1

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346 **Table 2:** Ocular Symptoms: described by patients. Two patients were children and four were
347 adults**.**
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Age	Sex	Symptom
8	F	eye pain
14	F	clear eye discharge
20	F	clear eye discharge
28	F	red eyes and blurred vision on the left
29	F	red eyes
46	M	blurred vision

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Table 3: Number of patients presenting with of other presenting complaints

Presenting Complaint	N	%	Confidence Intervals (%)
Cough	5	11	4-25
Abdominal pain	4	9	3-22
Chest pain	4	9	3-22
Itching	4	9	3-22
Insomnia	3	7	1-19
Fever	3	7	1-19
Loss of appetite	3	7	1-19
Laboured speech	2	5	1-15
Epigastric pain	2	5	1-15
Rash	2	5	1-5
17 other symptoms*	1	2	0-12

*Weight Loss, Hiccups, increased appetite, chest pain, sneezing, diarrhoea, vomiting, left sided weakness with facial nerve palsy, breathlessness, rash, dry flaky skin, earache, fever blister/cold sore, left scrotal swelling, nasal congestion, tremors

359 **Figure 2.**

360 A scale Venn diagram illustrating the overlap between the three main symptom groups.

361 Seven patients did not have any other the three main symptom groups.

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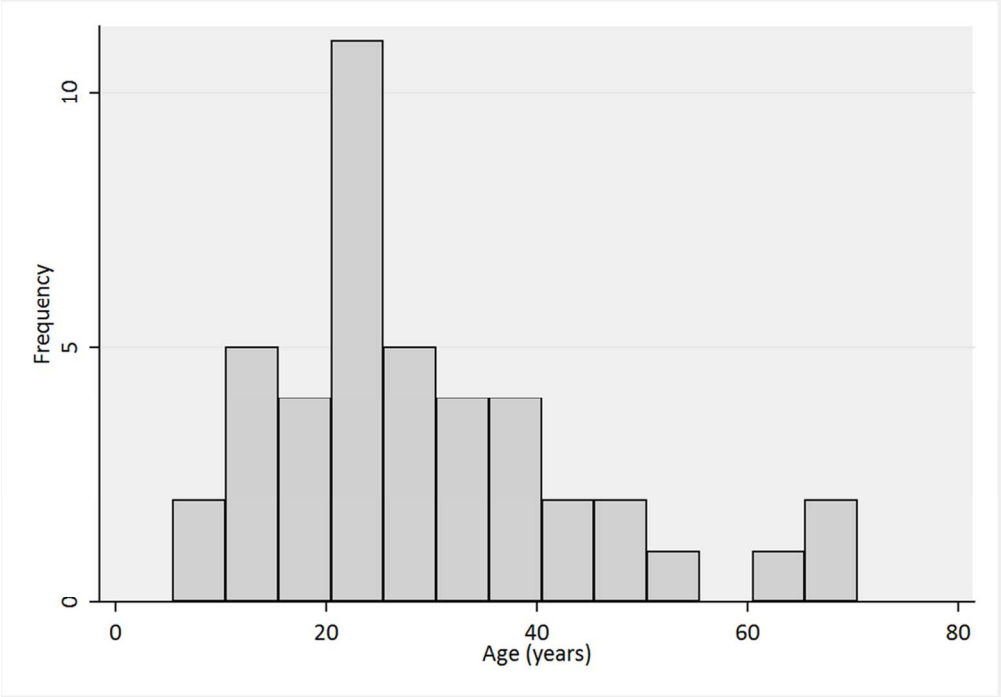

Figure 1. Age distribution of patients presenting to the 34th Military Hospital Ebola Survivor's Clinic.
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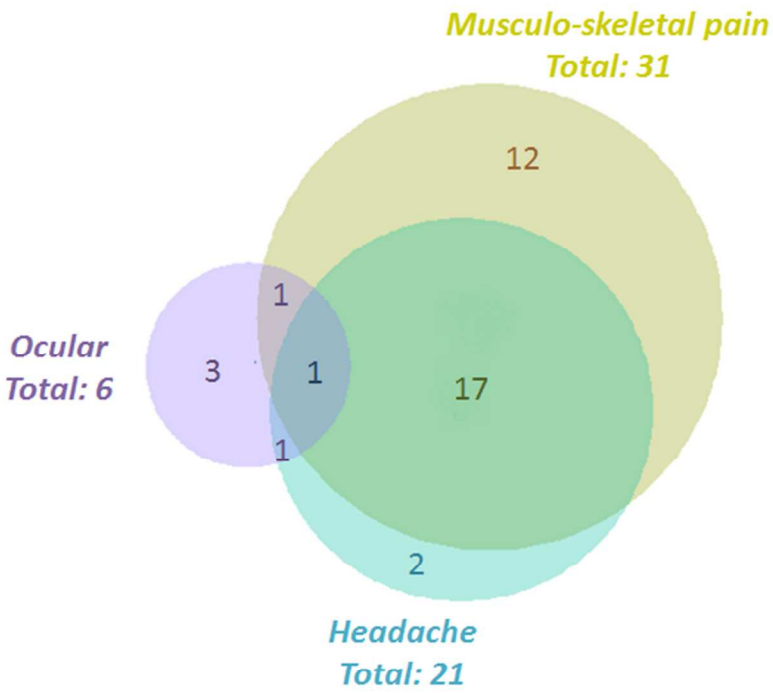

Figure 2. A scale Venn diagram illustrating the overlap between the three main symptom groups. Seven patients did not have any other the three main symptom groups.
117x99mm (300 x 300 DPI)