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Original Article

A rare case of *Salmonella* Paratyphi C osteomyelitis: A genetic analysis and review of *Salmonella* osteomyelitis in England

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ABSTRACT

Salmonella osteomyelitis is rare in patients without sickling hemoglobinopathies. Invasive disease caused by *Salmonella* Paratyphi C is rarer still with only one case reported in the United Kingdom in the last 15 years. We report a case of relapsing *S.* Paratyphi C osteomyelitis in a newly diagnosed diabetic patient from Ghana. Our patient was initially treated successfully with surgical debridement followed by 6 weeks of IV ceftriaxone before recrudescence 9 months later. Due to the rarity of *S.* Paratyphi C and the lack of recent travel, genomic analysis was undertaken to assess possible sources with the closest related strain being from Cote d'Ivoire. The patient had likley picked up the strain several years before presentation. We review current *Salmonella* osteomyelitis literature and audit all cases referred to the England and Wales *Salmonella* national reference laboratory over the last 15 years.

1. Introduction

Salmonella is a gram-negative rod belonging to the family Enterobacteriaceae. Human infection is primarily caused by *Salmonella enterica subspecies enterica* which consists of over 2600 serovars [1,2]. Serovars Typhi and Paratyphi A, B (phenotypically referred to as biovar d-tartrate negative) [3], and C as well as Sendai are considered typhoidal. Serovars Typhi and Paratyphi A and B are the most common typhoidal *Salmonella* isolated in England associated with travel to endemic countries, but Paratyphi C is incredibly rare [4]. Although rare, serovar Paratyphi C pathogenesis is similar to Typhi, for example, it contains the *tviB* gene, encoding a Vi polysaccharide capsule [5] and is therefore clinically indistinguishable. Serovar Sendai was originally isolated from a patient in 1922 with "typhoid like illness" [6] and has shown to have genetically diverged from *S.* Paratyphi A [7] but is rarely isolated from clinical cases. Typhoidal *Salmonella* such as *S.* Typhi are exclusive to human hosts, though other serovars such as Paratyphi B and C have been found in animals [8,9] they are endemic in many developing countries and typically cause enteric fever, characterized by systemic illness and bacteremia.

Non-typhoidal *Salmonella* (NTS) occur worldwide and are a common cause of gastroenteritis, in <5% of cases NTS infection can also lead to bacteremia and invasive disease [2]. *Salmonella* is an uncommon cause of osteomyelitis in patients without sickling hemoglobinopathies [10] with most cases caused by *S.* Enteritidis, *S.* Typhimurium, and *S.* Typhi [11,12]. We describe a case of *S.* Paratyphi C osteomyelitis in a newly diagnosed diabetic patient without sickling disease. This is the first case of invasive *S.* Paratyphi C detected by the English national reference laboratory in over 15 years, and only the third case of *S.* Paratyphi C causing osteomyelitis in the literature to date [13–15]. We also report on the use of whole genome sequencing to establish a possible origin of the strain in the absence of recent travel history.

1.1. Clinical case

A 53-year-old lady of Ghanaian origin presented to a London hospital with a 2-week history of gradually worsening pain in her right wrist associated with fatigue, fevers, anorexia, and polydipsia. She had no other gastrointestinal symptoms. Her past medical history was unremarkable except for a new diagnosis of diabetes made 2 days prior to her presentation. She had no pets, worked as a cleaner, and lived with her family who were well. Her last foreign travel was to Ghana 3 years prior, where she stayed for several weeks visiting family. She recalled no fevers or diarrheal illness during her visit.

On initial assessment she was dehydrated and lethargic with a sinus tachycardia of 125bpm, blood pressure 166/87, temperature 36.8C, respiratory rate 23, and oxygen saturation of 98% with no oxygen requirement. On examination her lung fields were clear and

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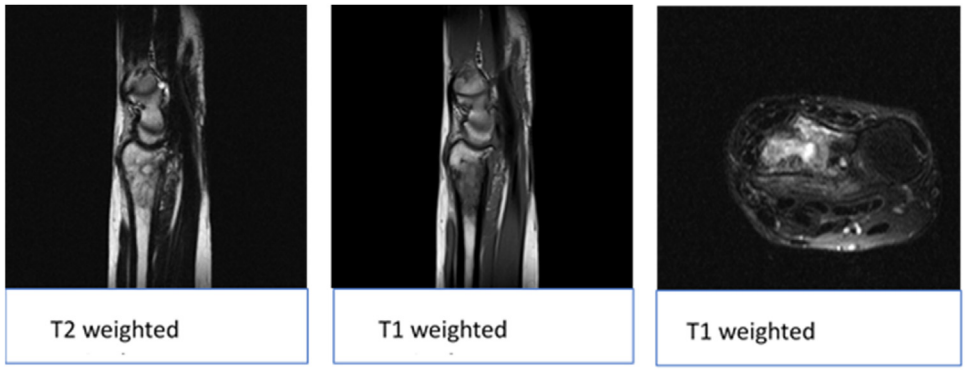

Fig. 1. Chronic osteomyelitis changes with interosseous abscess formation.

heart sounds unremarkable. Her neurology was intact, and abdomen soft and non-tender. Her right wrist was warm but not swollen or red, and the right radial head was painful on palpation, with passive movement of the wrist limited to 30 degrees in extension and 10 degrees in flexion.

Investigations revealed metabolic acidosis with a pH of 7.11, bicarbonate 11.0, lactate 2.7 with ketones and glucose on urinalysis. Blood tests demonstrated: CRP 87 mg/L, creatinine 110 μmol/L, urea 14.2 mg/dL, WCC 10.4 $\times$ 109/L, neutrophils 8.4 $\times$ 109/L, HbA1c 108 mmol/mol, LFTs unremarkable, HIV negative, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and myeloma screen negative, and immunoglobulins within normal range.

She was diagnosed with diabetic ketoacidosis (DKA) and possible osteomyelitis of the right distal radius. Blood cultures were sent, and she was managed as per DKA protocol and started empirically on Ceftazidime and Vancomycin. A plain film radiograph of the right wrist revealed lytic lesions at the radial head with surrounding leucancy suggestive of abscess formation. Blood cultures subsequently grew Gram negative rods in both bottles at less than 24 hours and her antibiotics were changed to ceftriaxone monotherapy after microbiology review.

1.2. Microbiology investigation

Aerobic and anaerobic blood culture bottles incubated on a BacTAlert VirtuO™ instrument were positive at 24 hours for gram negative rods. Non-lactose fermenting colonies grew on Cystine Lactose-Electrolyte-Deficient (CLED) and Columbian Blood agar which were identified as *Salmonella* species by matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. Antibiotic sensitivity was determined and slide agglutinations using *Salmonella* antisera gave positive reactions for PSO, PSH 1&2, and O-6,7. The Isolate (848979, November 2019) was sent to the Public Health England Gastrointestinal Bacteria Reference Unit (GBRU) where it was confirmed as *Salmonella* enterica subspecies enterica (I) serovar Paratyphi C (eBURST group 20, sequence type 146) by whole genome sequencing (WGS) using Metric Orientated Sequence Type (MOST) [16] methodology compared against the *Salmonella* MLST database [17], as previously described [18,19]. Antimicrobial resistance determinants (AMR) were identified using Gene finder [20] and revealed a single *parC* gene mutation (*parC*_[57:T-S], MIC = <0.015 mg/L) in the quinolone resistance-determining region (QRDR), which does not confer resistance to ciprofloxacin [20]. Phenotypic sensitivity was confirmed by MIC testing using Mueller-Hinton agar dilution to amoxicillin, ceftriaxone, ceftazidime, ertapenem, ciprofloxacin, gentamicin, azithromycin, tetracycline, fosfomycin, trimethoprim, colistin, chloramphenicol according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) defined breakpoints [4,21]

1.3. Further investigation and management

The patient continued ceftriaxone monotherapy with good clinical improvement. Repeat blood cultures showed no growth, an ultrasound of her abdomen was unremarkable and electrophoresis revealed no hemoglobin abnormalities. Followup MRI imaging of the wrist revealed a complex 4 cm soft tissue mass abutting the distal radius with a fluid component and edema suggestive of osteomyelitis with abscess formation (Fig. 1). On day 11 of her hospital stay, operative bone debridement with abscess wash out was performed; all 3 interoperative bone samples were negative on prolonged culture and 16S PCR testing.

1.4. Outcome / relapse

The patient completed a further 6 weeks of IV ceftriaxone 2 g once daily as an outpatient. She remained well and received regular orthopedic follow-up until she was readmitted 9 months later with reoccurring pain at the right wrist. A repeat MRI showed a small residual fluid-filled cavity in the right distal radius with surrounding remodeling suggestive of chronic osteomyelitis with abscess formation. Drilling and curettage were performed, and samples obtained intraoperatively were culture positive for a *Salmonella* spp. The isolate (997084, September 2020) underwent whole genome sequencing at the GBRU and was again identified as *Salmonella* enterica subspecies enterica (I) serovar Paratyphi C (eBURST group 20, sequence type 146), confirming disease recrudescence. The patient was reinitiated on Ceftriaxone and referred to a tertiary center specializing in bone and joint infections.

1.5. Genetic investigation of isolate origin

Due to the rarity of S. Paratyphi C in the UK, a review of national laboratory data between 2004 and 2020 reported by PHE was reviewed and any viable *S.* Paratyphi C historical isolates were tested by PCR [5] to select strains for WGS for comparative analysis. ST, eBURST Group (eBG), and serotype were determined from the genome data [16,17].

Genomic analysis of the population structure of *S.* Paratyphi C was undertaken to ascertain associations with other global isolates in Enterobase (https://enterobase.warwick.ac.uk/). Core genome multilocus sequence typing (cgMLST) analysis was performed as previously described [22] using the cgMLST V2 HierrCC V1 algorithm [23]. The minimum spanning tree was created in Enterobase for each pathogen using the MSTreeV2 algorithm [23] and visualized using GrapeTree [24] (Fig. 2). Hierarchical Clustering was analyzed at the 5 alleles level (HC5 – strains linked within 5 cgMLST alleles) for trend analysis in association with country of origin.

FASTQ sequences were deposited in the National Center for Biotechnology Information Short Read Archive (SRA) under the BioProject

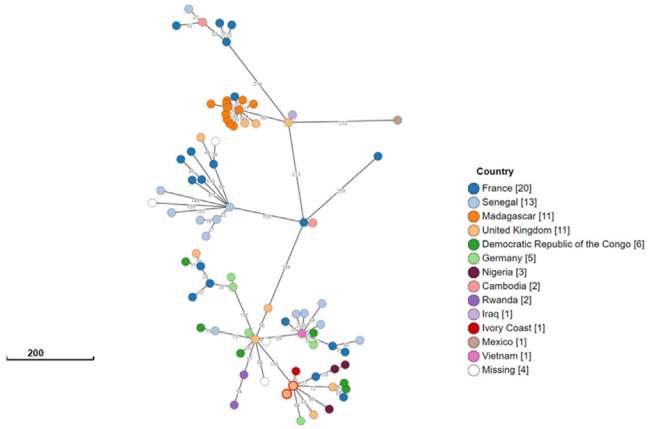

Fig. 2. GrapeTree of cgMLST (3002 loci) from 81 genomes of ST146 (S. Paratyphi C) in EnteroBase, consisting of all ST146 genomes assembled by EnteroBase from the ENA short-read archives, including the genomes from UKHSA (generated 10/12/2020). Scale bar for 200 loci at right and number of loci between isolates are stated on the branches. Isolates from S. Paratyphi C osteomyelitis isolates are circled in red with the closest related strain, 15 alleles different, from the Ivory coast isolate from 1989.

PRJNA315192, reference SRR10604714. The second isolate from bone (997084) was submitted to the National Collection of Type Cultures.

2. Results

cgMLST sequence type of isolates was ST21800 and HC5_218100 (at the hierarchical cluster 5 allelic level). The closest identified strain (89_13) was isolated from a patient in the Ivory Coast in 1989 (15 alleles difference from the case study strain) (Fig. 2).

2.1. *Epidemiology of* Salmonella *osteomyelitis – national audit results*

A national review of *Salmonella* osteomyelitis in England and Wales was undertaken by searching the Public Health England (PHE) Gastrointestinal data Warehouse (GDW) [18,19] for cases of query *Salmonella* osteomyelitis submitted from hospitals across England and Wales from 2004 to 2020 (Table 1). Clinical Information was obtained from the submitted request forms, and historical isolates (pre-WGS, before 2014) were revived and sequenced to assess the diversity of isolates via single nucleotide polymorphism (SNP) single linkage cluster typing [25]. We included all bone, blood, joint fluid, and deep tissue isolates that cultured *Salmonella* and were associated with a clinical history suggestive of osteomyelitis. Wound swabs and stool samples that were not linked to other isolates of the above criteria were excluded. Cases are presented in Table 1. Fifty-two isolates from 33 cases were identified over the 16-year period, accounting for only 0.02% of *Salmonella* isolates referred during the same time (n = 17,5135). Isolates were from both males and females, across all age groups, and from different bone types. Five cases were detailed to have a sickling hemoglobinopathy and only 4 patients had a documented recent travel history. There was a variety of *Salmonella* serotypes causing osteomyelitis and the diversity of strains isolated from the same patient was small; varying between 0 and 10 SNPs according to single linkage clustering methods (Table 1).

3. Discussion

3.1. *Epidemiology*

Osteomyelitis is the most common infectious complication of sickling hemoglobinopathies with prevalence estimates of 12% to 17.8% [26] with *Salmonella* the most common causative organism in European and American populations [27]. The prevalence of *Salmonella* osteomyelitis in an unselected population is much lower. In a pre-antibiotic era review performed by Murphy et al. only 164/18,840 (0.84%) of patients with typhoidal fever were found to have osteomyelitis, and several recent osteomyelitis diagnostic and treatment studies failed to isolate *Salmonella* as a causative pathogen in any of the reported cases [28,29].

The largest review of *Salmonella* osteomyelitis to date was performed by Cohen et al. on cases presenting to 2 American hospitals as well as previously published cases between 1976 and 1984 [12]. They found that 60/150 total cases suffered from hemoglobinopathies and 7/150 were diabetic. Fever was present in the vast majority at presentation and the most common sites of infection were the long bones and lumbar vertebra, with the radius involved in 15/150 (10%). Of 121 cases with an identified serovar, 28 (23%) were typhoidal and only 2 were caused by *S*. Paratyphi C [12]. In areas where *S*. Typhi and *S*. Paratyphi are endemic it is unsurprising that a greater proportion of extra-intestinal infection is caused by typhoidal strains, as evidenced by Rohilla et al. [30] who described 20 cases of *Salmonella* osteomyelitis in India between 2010 and 2018, of which 19 were caused by *S*. Typhi.

UK data is currently limited to case reports and a single retrospective series performed by Ispahane et al. which recorded 134 cases of invasive *Salmonella* from a total of 6546 patient episodes of bacteremia between 1980 and 1997. Of those with *Salmonella*, osteomyelitis was seen in 2 children and 3 adults (4% of all invasive cases), of whom one had sickle cell anemia, and 2 were immunocompromised [31].

Contemporary data detailing the causative serovars of *Salmonella* osteomyelitis in a UK setting is lacking. To address this, we interrogated the PHE data-base to identify referred isolates from cases compatible with *Salmonella* osteomyelitis. A total of 33 cases were identified; interpatient strains were diverse however the majority were NTS serovars except in those with travel to areas where typhoidal *Salmonella* is endemic. The most common causal serovars of osteomyelitis (*S*. Typhimurium and *S*. Enteritidis) are also the most common causes of gastroenteritis outbreaks and sporadic cases in the UK [18,19], The diversity of isolates from the same patient was small and varied between 0 and 10 SNPs according to single linkage clustering methods as detailed in Table 1.

3.2. *Clinical*

Infection with NTS serovars typically results in self-limiting enteritis, in contrast, infection with typhoidal serovars usually causes systemic illness characterized by fever with or without abdominal pain [2], although it is not possible to differentiate the clinical presentations of different serovars within the typhoidal and nontyphoidal classifications and require microbiological identification [5]. Both typhoidal and nontyphoidal *Salmonella* organisms adhere to and penetrate the small bowel epithelium, however, a damped IL8 response to typhoidal serovars limits neutrophil migration and mucosal inflammation and allows invasion of the submucosa where they proliferate within mononuclear cells [32]. They then disseminate via the lymphatic or hematogenous route and can cause focal infection at distal sites including osteomyelitis [31], as described here. A small minority of patients can become chronic carriers of *Salmonella*, with persistence of organisms in the gut for >12 months. Using WGS, we found that the strain of *S*. Paratyphi C, in this case, was most closely related to an isolate from West Africa (Fig. 2), and postulate that this was likely acquired while the patient was in Ghana. This would mean that there was a minimum of 3 years between likely exposure and the onset of symptoms; suggestive of persistent gut carriage, with active infection, later triggered by the onset of uncontrolled diabetes [33]. Our patient also had a recrudescence of osteomyelitis despite apparent cure; a well described phenomenon in typhoidal *Salmonella*, caused by the persistence of bacteria within macrophages at “sanctuary sites” such as the liver, spleen, and bone marrow after treatment [34]. This has also been reported in *S*. Paratyphi C specifically, in a case of abdominal infection [35] and a well a case of tibial osteomyelitis, in which infection reoccurred in the contralateral tibia seventeen years after the patient’s first presentation [13].

Table 1
Table summarising patients with presumptive or confirmed Salmonella Osteomyelitis infections (2004–2020).

Patient No.	Sex	AGE (at first sample)	Foreign Travel	Year of sampling	Clinical Information on request form	Source of isolate	Organism identified	Phage type	eBG	ST	SNP address
1	M	30	N	2004	Osteomyelitis	Bone (Right Tibia)	*Salmonella* Enteritidis	PT 6a	4	11	1.1.2.2821.4568.6768.16370
2	M	26	Pakistan	2004	Osteomyelitis Tibia. (Had enteric fever 18 months ago)	Bone (material from Tibia)	*Salmonella* Typhi	PT E1	–	–	–
3	F	18	Not Stated	2004	Osteomyelitis	Bone (Left Humerus)	*Salmonella* Uganda	–	–	–	–
				2004	Not stated	Wound swab	*Salmonella* Uganda	–	–	–	–
				2004	Not stated	Wound Swab	*Salmonella* Uganda	–	–	–	–
4	M	12	N	2004	Osteomyelitis?/ Known sickler, pain in joints/ septic arthritis/fever	Blood	*Salmonella* Enteritidis	PT 8	4	310	1.2.3.2823.4573.6774.16382
5	F	8	Not stated	2005	Osteomyelitis	Chest Wall Swab	*Salmonella* Colindale	–	296	584	–
6		Not stated	Nigeria	2005	Osteomyelitis	Blood	*Salmonella* Montevideo	–	40	2328	105.134.211.247.275.290.326
7	F	62	N	2007	Osteomyelitis	Blood	*Salmonella* Durham	–	–	–	–
8	M	57	Not stated	2008	Not stated	Abscess chest wall	*Salmonella* Typhimurium	DT 12	138	36	10.15.92.472.602.657.739
				2009	Osteomyelitis	Chest Swab	*Salmonella* Typhimurium	Un-typable	138	36	10.15.92.472.602.659.741
				2009	Osteomyelitis	Rib tissue	*Salmonella* Typhimurium	–	138	36	10.15.92.472.602.660.742
9	M	44	Not stated	2008	Osteomyelitis/Myelo-proliferative disorder	Subperiosteal collection	*Salmonella* Typhimurium	DT 193	1	19	31.50.83.86.5753.7071.10231
10	M	23	Not stated	2008	Osteomyelitis	Tissue	*Salmonella* Enteritidis	PT 51	4	11	1.1.2.28.4567.6767.16368
11	F	19	Not stated	2008	Right Knee Arthroscopy	Right Knee Swab	*Salmonella* Enteritidis	PT 21	4	11	1.1.2.80.4574.6775.16383
				2008	Osteomyelitis	Tissue - Right Femoral canal	*Salmonella enterica* O rough:g,m:-	–	–	–	–
12	M	58	Not stated	2009	Osteomyelitis	Wound swab	*Salmonella* Enteritidis	PT 4	4	11	1.1.2.2819.4563.6762.16360
13	F	31	Not stated	2009	Osteomyelitis and sickle cell disease	Pus - left femur	*Salmonella* Stanleyville	–	–	–	–
14	M	10	N	2009	Osteomyelitis?	Blood	*Salmonella* Oslo	–	–	–	–
				2009	Osteomyelitis?	Faeces	*Salmonella enterica* 6, 7:-:e, n, x	–	–	–	–
15	M	9	Not stated	2009	Knee septic arthritis, Osteomyelitis?	Right Knee fluid	*Salmonella* Typhimurium	DT 56	1	313	–
				2009	Sickle Cell Crisis, isolated from Blood culture and Knee aspirate	Right Knee Aspirate	*Salmonella* Typhimurium	DT 56	1	313	1.37.55.144.5756.7074.10234
16	M	7	N	2009	Osteomyelitis/ Sickle Cell disease?	Left Femoral Wound	*Salmonella* Typhimurium	DT 56	1	313	1.37.55.2627.5758.7076.10237
17	F	0	Not stated	2009	Osteomyelitis?	Blood	*Salmonella houtenae* 44:z4, z23:-	–	–	–	–
				2009	Bloody diarrhoea	Faeces	*Salmonella houtenae* 44:z4, z23:-	–	–	–	–
18	F	4	Jamaica	2010	Arm pain, Osteomyelitis, Sickle Cell Disease	Blood	*Salmonella* Hartford	–	169	2586	–
19	M	1	Not stated	2010	Osteomyelitis?	Faeces	*Salmonella arizonae* 13,23:z4,z23:-	–	218	1422	–

(*continued on next page*)

Table 1 (*Continued*)

Patient No.	Sex	AGE (at first sample)	Foreign Travel	Year of sampling	Clinical Information on request form	Source of isolate	Organism identified	Phage type	eBG	ST	SNP address
20	F	44	Not stated	2011	Osteomyelitis of right ankle/Septic arthritis	Ankle Aspirate	*Salmonella* Typhimurium	DT 12	1	19	1.18.231.2621.5746.7062.10216
				2011	Not stated	Tissue	*Salmonella enterica* O rough:i:1,2	–	–	–	–
21	M	25	N	2012	Osteomyelitis of radius	Wound swab	*Salmonella* Typhimurium	Un-typable	–	–	–
22	M	16	Not stated	2012	Osteomyelitis	Tissue - Right Humerus (Revision)	*Salmonella* Stanleyville	–	361	2562	–
23	M	12	N	2012	Osteomyelitis?	Hip Aspirate	*Salmonella enterica* 30:y:l,w	–	ND	2730	–
				2012	Osteomyelitis?	Hip Aspirate	*Salmonella enterica* 30:y:l,w	–	ND	2730	–
				2012	Osteomyelitis?	Faeces	*Salmonella enterica* 30:y:l,w	–	ND	2730	–
24	M	12	Not stated	2012	Osteomyelitis	Pus swab	*Salmonella* Livingstone	–	–	–	–
				2012	Osteomyelitis	Tissue	*Salmonella enterica* 6,7:d:-	–	–	–	–
25	M	4	N	2012	Osteomyelitis?	Faeces	*Salmonella* Braenderup	–	–	–	–
26	M	37	Not stated	2013	Bone infection	Pus right femur	*Salmonella* Enteritidis	PT 4	4	11	1.1.2.28.4564.6763.16361
				2013	Osteomyelitis right femur	Tissue - right thigh	*Salmonella* Enteritidis	PT 4	4	11	1.1.2.28.4564.6763.16361
27	F	31	N	2014	Osteomyelitis	Humerus Tissue	*Salmonella* Typhimurium	DT 208	1	19	1.4.516.2622.5748.7064.10218
				2014	Osteomyelitis	Humerus Tissue	*Salmonella* Typhimurium - monophasic	–	1	19	1.4.516.2622.5748.7065.10219
				2014	Chronic osteomyelitis, discharge	Shoulder Swab	*Salmonella* Typhimurium - monophasic	–	1	19	1.4.516.2622.5748.7065.10228
28	M	12	Greece	2015	Osteomyelitis	Faeces	*Salmonella* Brandenburg	–	12	65	5.7.7.7.7.7.47
				2016	Osteomyelitis	Hip Joint	*Salmonella* Brandenburg	–	12	65	5.7.7.7.7.7.7
29	F	12	Not stated	2015	Osteomyelitis	Wound swab foot	*Salmonella* Newport	–	3	45	56.68.83.91.93.96.100
30	M	19	Not stated	2016	Osteomyelitis	Tissue - Left Femur	*Salmonella* Ealing	–	ND	5027	–
31	F	4	Not stated	2016	Osteomyelitis	Bone Biopsy	*Salmonella* Nima	–	ND	5024	Not snpdb-able ebg/st
32	U	39	Not stated	2017	Osteomyelitis Right Arm	Pus	*Salmonella* Typhi	–	13	1	1.104.149.170.321.521.777
33	F	46	N	2018	Osteomyelitis distal femur	Pus from left Knee	*Salmonella* Schwarzengrund	–	33	96	1.15.15.15.15.15.15
34	F	46	N - Ghana 3 years prior	2019	Diabetic Ketoacidosis	Blood	*Salmonella* Paratyphi C	–	20	146	–
				2020	Previous history of *Salmonella* osteomyelitis	Distal Radius, right side bone	*Salmonella* Paratyphi C	–	20	146	–

Key: - where the test has not been undertaken or not applicable for sequencing or phage typing, ND - Not determined, where the eBURST group (eBG) is not currently defined with the sequencing type (ST).

The treatment of *Salmonella* osteomyelitis is beyond the scope of this report and owing to the rarity of the condition there is a paucity of specific evidence available, but usually involves surgical debridement followed by antibiotic therapy targeted to the organism's susceptibility [26].

4. Conclusion

In conclusion, we report the first case of invasive *S.* Paratyphi C recorded in the UK for over 15 years, and only the third case of *S*. Paratyphi C osteomyelitis to be described in the literature [13–15]. This case shows the importance of a good travel history with consideration of chronic carriage and highlights the risk of disease relapse even after aggressive debridement and appropriate antibiotic treatment. *Salmonella* osteomyelitis remains rare in the UK, and the majority of cases are caused by NTS, however, in patients with appropriate travel history, typhoidal strains should be considered.

Consent for publication

Written informed consent was given for publication by the patient described in the case study portion of this article.

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Declaration of competing interest

WH has received speaker fees from Gilead Sciences.

Author contributions

WH, JS and **MC** conceptualised this report; **WH** and **JS** collected retrospective patient metadata; Microbiological work up and genetic analysis was performed by **JH, GG** and **MC; WH** and **MC** wrote the original draft, all authors revised, read and approved the final manuscript.

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