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PERSONAL VIEW

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Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS): diagnosis, surveillance and public-health management in England

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In November 2019, on behalf of Public Health England (PHE), the authors invited a diverse group of healthcare and public-health professionals, from the fields of microbiology, nephrology and epidemiology, to a Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS) workshop, chaired by Professor Nick Phin. The aim of the workshop was to highlight the challenges associated with the diagnosis, surveillance, and clinical and public-health management of this rare, but potentially fatal condition. Here, we present a personal view of the discussion and recommendations.

HUS is characterized by a triad of symptoms: microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury. Most cases of HUS (90%) occur as a single episode following infection with STEC [1]. Long-term follow-up of patients is recommended as it is estimated that 25–30% of HUS cases are left with chronic sequelae, including reduced glomerular filtration rate, hypertension or proteinuria, neurological symptoms or end-stage renal disease [2, 3]. Atypical HUS (aHUS) is recurrent and occurs due to abnormalities in the alternative complement regulatory pathway, resulting in endothelial cell damage and causing microvascular thrombosis. Prior to the availability of a drug called eculizumab, a recombinant mAb that acts against the complement protein C5, the prognosis for aHUS was poor [4]. Eculizumab has improved outcomes of aHUS cases, but treatment has adverse side effects, is life-long and expensive (www.nice.org.uk/news/press-and-media/high-cost-of-treatment-for-rare-blood-disorder-needs-to-be-clarified-says-nice-in-draft-guidance) [5]. The treatment recommendation for STEC-HUS is best supportive care, focusing on renal and fluid replacement therapy to restore circulating volume and reduce ischemic or hypoxic tissue damage, and treatment of renal, cardiac and neurological complications [6, 7]. The treatment dichotomy for aHUS and STEC-HUS, and the implications for clinical and public-health management, therefore, mandates early diagnosis of STEC infection.

Outbreaks of STEC-HUS in England in the 1980s were caused by STEC O157:H7 and laboratory protocols, therefore, focused on the use of selective agar for this STEC serotype. PCR detects all STEC serotypes, and since 2013 there has been a significant increase in the detection of serotypes other than STEC O157 (non-O157 STEC) detected in England corresponding with the number of laboratories implementing the PCR assay [8, 9]. Analysis of clinical outcome data has shown that non-O157 STEC have the potential to cause severe gastrointestinal symptoms, including bloody diarrhoea, abdominal pain and vomiting, and HUS [10]. At the time of the workshop, it was estimated that around 20% of local hospital laboratories in England were using PCR for detection of STEC. The implementation of a PCR assay capable of detecting all STEC serotypes in all PHE regional laboratories is scheduled for 2020. This initiative will increase the capacity of hospital laboratories in the UK to offer rapid, sensitive, near-patient testing for the diagnosis of STEC-HUS, including those cases caused by non-O157 STEC. If PCR is not available at the local or regional hospital diagnostic laboratory, specimens from patients with symptoms of HUS should be rapidly referred to the Gastrointestinal Bacteria Reference Unit (GBRU) at PHE (Table 1) [11, 12]. The implementation of PCR at the local-hospital level will enable the testing of all faecal specimens from hospital in-patients and community cases reporting to primary healthcare; thus, facilitating the identification of individuals infected with STEC prior to the development of symptoms of HUS.

Although outbreaks of STEC-HUS are rare, they can have a devastating impact on the families involved. Failure to obtain an accurate, timely diagnosis of STEC-HUS has a detrimental effect on prompt notification to PHE; thus, delaying effective public-health action with respect to contact tracing and

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Abbreviations: aHUS, atypical haemolytic uraemic syndrome; GBRU, Gastrointestinal Bacteria Reference Unit; HUS, haemolytic uraemic syndrome; NESSS, national enhanced surveillance system for STEC; PHE, Public Health England; STEC, Shiga toxin-producing *Escherichia coli*.

Table 1. Considerations for laboratory diagnosis of STEC amongst HUS cases

The scenario	The problem	The solution
PCR is not available at the local hospital laboratory	Non-O157 STEC will not be detected.	Rapid referral of specimens to the PHE GBRU laboratory
The patient was treated with antibiotics	Antibiotics kill viable organisms causing a false-negative culture result	Obtain a faecal specimen prior to administering antimicrobial therapy AND/OR sample and test household contacts to aid diagnosis
The patient is constipated	It is not possible to obtain a faecal specimen for testing and diagnosis of STEC	Take a rectal swab for testing AND/OR sample and test household contacts to aid diagnosis

preventing ongoing transmission. Outbreaks of HUS caused by non-O157 STEC are particularly challenging, as evidenced by a recurrent outbreak of STEC O55:H7 in England that occurred between 2014 and 2018 [9, 13]. The source of the causative organism has still not been identified, although evidence suggests that transmission to the human cases had occurred via exposure to environmental contamination. Clinical outcomes in symptomatic individuals, median age of just 4 years old, were severe with over 50% of symptomatic cases linked to this outbreak developing STEC-HUS. The severity of illness associated with this outbreak, particularly in the very young, was typified in 2018, when there were two fatal cases in siblings both under 5 years old. As with previous outbreaks, delays in notification and diagnosis of STEC-HUS were identified as challenging aspects of the investigation.

Delays and failures to notify suspected cases of STEC-HUS were not unique to this outbreak. It is a statutory duty to report STEC and HUS under the Health Protection (Notification) Regulations (2010). At PHE, we operate a national enhanced surveillance system for STEC (NESSS) that collects standardized clinical, microbiological and epidemiological data from all cases of STEC in England, and reconciles microbiological data from specimens submitted to GBRU with surveillance data collected on the enhanced surveillance questionnaire [14]. Despite this level of enhanced surveillance, there is evidence of under ascertainment of STEC-HUS and it is estimated that, overall, just over a third of all STEC-HUS cases (36.2%) in England are captured by NESSS (PHE unpublished in-house data). Every year, NESSS also identifies additional suspected STEC-HUS cases diagnosed clinically without microbiological confirmation. Between 2009 and 2017, this included 149 such cases, which could have potentially been misdiagnosed as aHUS. Reasons for not confirming STEC infection in cases of STEC-HUS include failure to take the appropriate specimens (faeces or rectal swab), failure to request PCR testing and administering antibiotic treatment before taking specimens for microbiological analysis (Table 1). Antibiotics are contraindicated for the treatment of HUS, but are sometimes administered when the patient presents to primary healthcare, prior to diagnosis [1]. For public-health action to be timely and effective, prompt notification and rapid testing of the appropriate specimens by PCR are critical.

In summary, for both clinical management of individual patients and for public-health risk assessment, early ascertainment of STEC infection is required. A diagnosis of STEC-HUS should be considered in any patient developing thrombotic microangiopathies, particularly if it follows a diarrhoeal illness and is associated with acute kidney injury. However, aHUS also may be associated with diarrhoea, and not all STEC-HUS cases report a diarrhoeal prodrome [1]. Therefore, STEC infection should be confirmed or ruled out by PCR and/or culture of a faecal specimen (or rectal swab if a faecal specimen is not available) early in the care pathway, before administering antibiotics (Table 1) [15–17]. Deployment of the PCR will reduce the potential for misdiagnosis of patients with HUS, and ensure that the appropriate treatment regimens for STEC-HUS (best supportive care) and aHUS (eculizumab) are initiated early in the care pathway. Moreover, timely diagnosis will ensure prompt notification of cases of STEC-HUS for public action, including outbreak detection and investigation, and improve surveillance.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
The authors declare that there is no requirement for ethical approval for this submission.

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