Algorithms for the local response to cases of STEC infection
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Algorithms for the local response to cases of STEC infection

Since 2013, many local NHS laboratories have introduced real-time Polymerase Chain Reaction (RT-PCR) testing kits as a gastrointestinal (GI) screening panel for faecal samples where infectious disease is suspected. These PCR GI panels include primers that detect shiga toxin (stx) genes (stx1 and stx2) that are possessed by all STEC. The introduction of stx PCR tests by a diagnostic laboratory is likely to lead to an increase in the number of STEC infections detected (O157 and non-O157) and consequently an increased number of notifications to local Health Protection Teams (HPTs). Evidence of the public health impact of different non-O157 STEC is still emerging and a universal approach to the public health management of all stx positive results is not appropriate.

Local stx PCR positive but culture negative samples should be sent to the Gastrointestinal Bacteria Reference Unit (GBRU) for further investigation and various non-O157 STEC serogroups may be identified. Referral of local culture negative samples is especially important for those with bloody diarrhoea and Haemolytic Uraemic Syndrome (HUS).

The ultimate aim of the public health response is to prevent disease and transmission associated with STEC infections. This is relatively rapid and straightforward for STEC O157 infections because following an stx PCR positive result, local laboratories can proceed to test for and isolate O157 strains with reports of presumptive E. coli O157 infections usually available within 3 days of specimen collection, enabling the public health response to be commenced quickly.

However, E. coli O157 is not grown from the vast majority of stx PCR positive specimens and since local laboratories cannot routinely isolate non-O157 STEC, there is a delay in confirmation with full laboratory results. Serotype and stx subtypes are usually reported by GBRU about 2-3 weeks after the HPT is first informed of the case.

The main aim of the public health response to cases is to prioritise the response to those cases most likely to be infected with viable STEC belonging to non-O157 HUS associated E. coli (HUSEC strains). This is likely to represent around 3% of all cases with stx PCR positive results, or 10% of all non-O157 STEC serotypes isolated.

In the interim, local PCR and culture results, followed by GBRU in-house PCR results may be available. The following algorithms have therefore been divided into 3 stages based on this process to provide HPTs with guidance on how to respond to cases when each new piece of information becomes available.
The aim is to provide a proportionate public health response that protects the public’s health whilst taking into consideration the workload implications for HPTs/local authorities, without imposing unnecessary restrictions on individuals.

The three algorithms are based on laboratory results as they become available as follows:

- **Stage 1** - Diagnostic laboratory results (PCR and culture) and clinical history (HUS/bloody diarrhoea)
- **Stage 2** – GBRU in-house PCR results (\textit{stx} and \textit{E. coli} attachment and effacing (\textit{eae}) gene)
- **Stage 3** – GBRU serogroup/serotype including \textit{stx} subtypes

The algorithms should be used for the investigation of single cases and is colour coded for public health management as follows:

- **Red** – full / majority of public health actions recommended
- **Amber** – limited public health actions recommended
- **Green** – warn and inform public health actions only, or no public health actions
- **Blue** – questions for decision making process
- **White** – information only

The algorithms cover HUS and all STEC infections (O157 and non-O157). The STEC O157 public health management is described in the first part of this guidance and you will find references to HUS and O157 results in the algorithm sections that follow. This is to give a complete picture of results that come back to HPTs, but will direct you to the STEC O157 public health management where appropriate.

The algorithms should be used in conjunction with the following sections of this guidance as appropriate:

- Section 2 - Public health management of STEC O157 (pages 33-38)
- Section 3 – The principles of the public health management of \textit{stx} PCR positive results and non-O157 STEC (pages 41-44)
There are several ways potential STEC infections are reported to the HPT:

- Local culture *E. coli* O157 positive
- Notification of HUS
- Symptomatic contact with an epidemiological link to another case with HUS, or culture confirmed O157 STEC, or culture confirmed non-O157 STEC belonging to HUSEC strain *(stx2a/2c/2d and eae/aggR)*
- Local stx PCR positive, but local culture negative for *E. coli* O157
- Symptomatic contact with an epidemiological link to another case with culture confirmed potential HUSEC strain *(stx2 and eae)*
- Symptomatic contact with an epidemiological link to another case infected with culture confirmed lower risk STEC strain *(non stx2a/2c/2d)*

For notifications of infective bloody diarrhoea, unless there is a known epidemiological link to a case with HUSEC/potential HUSEC strain infection, public health action can usually wait until the local diagnostic laboratory culture results are known. If local laboratories are using PCR, initiation of public health action should follow locally agreed arrangements.

**Note 2**

Local culture *E. coli* O157 positive OR history of HUS

- Define case as PROBABILE
- Full public health actions as per O157 management for case and contacts are recommended

**Rationale**

Most cases of diarrhoea associated HUS are caused by STEC belonging to HUSEC strains.

Symptomatic contact with an epidemiological link to another case with HUS, OR culture confirmed STEC of HUSEC strain, including O157 *(stx2a/2c/2d and eae/aggR)*

- Define case as PROBABILE
- Full public health actions as per O157 management for case and contacts are recommended

**Rationale**

There is evidence of potential transmission of HUSEC strain between the case and this symptomatic contact.

**Note 3**

Local stx PCR positive, local culture *E. coli* O157 negative

This is the usual result received by HPT and is the usual starting point of the response. Result may be received by phone call or SGSS import to HPZONE.

- Clinical and demographic information should be reviewed.

**Rationale**

*stx* PCR tests are very sensitive and specific. If positive DNA containing *stx* genetic material is present. The test does not distinguish between viable and dead non-viable organisms or even free *stx*-bacteriophages in the faeces. To date the experience of HPTs regularly receiving these results is that GBRU does not confirm STEC infection in about 30% of specimens. STEC strains are isolated from 40% of specimens and 20% of specimens are *stx* positive but STEC is not recoverable. About 3% of
local stx PCR positive results are finally confirmed by GBRU as STEC belonging to HUSEC strains other than O157 STEC.

**Note 4**

Symptomatic contact with an epidemiological link to another case with potential HUSEC strain (stx2 and eae regardless of stx1)
- Follow the actions for cases with history of bloody diarrhoea (Note 8).

**Rationale**
The case associated with this symptomatic contact may not subsequently be confirmed by GBRU to be a HUSEC strain. The implementation of pragmatic precautions (exclusion while symptomatic and providing hygiene advice) and the completion of the STEC questionnaire (information about potential transmission and contacts) aims to balance the risk of transmission against imposing restrictions on the case that may not be necessary.

**Note 5**

Symptomatic contact with an epidemiological link to another case with lower risk strain (non stx2a/2c/2d)
Define case as PROBABLE
- Arrange diagnostic sample, give hygiene advice, provide PCR letter/leaflet if not already done and exclude until minimum of 48 hours symptom free
- Public health actions determined by diagnostic result.

**Rationale**
There is an epi link is to another case with a lower risk strain. The likelihood of serious illness or outbreaks is low, manage like other non STEC gastrointestinal infections.

**Note 6**

Local stx PCR positive, local culture E. coli O157 negative with history of HUS or epidemiological link to case infected with HUSEC strain
- Stx PCR positive and HUS, define case as CONFIRMED or
- Epidemiological link, define case as PROBABLE
- Full public health actions as per O157 management for case and contacts are recommended.

**Rationale**
Current case is stx PCR positive and is a contact of another case infected with a HUSEC strain. There is evidence of possible transmission.
- or case of diarrhoea associated HUS (D+ HUS), most cases of D+ HUS are caused by a HUSEC strain of STEC.

**Note 7**

Local stx PCR positive, local culture E. coli O157 negative no history of HUS and no epidemiological link to case infected with HUSEC strain
- Review history for features of severe disease – bloody diarrhoea or admission for acute diarrhoeal illness. Depending on local arrangements this information may be on laboratory request form or provided by reporting clinician/microbiologist.
• In the absence of this information the HPT should consider contacting the clinician who arranged for the test to confirm the history.

**Note 8**

Local stx PCR positive, local culture *E. coli* O157 negative with history of bloody diarrhoea

History of bloody diarrhoea or admission with acute diarrhoeal illness has been reported on the laboratory result report or by the clinician/microbiologist:

• Define case as PROBABLE
• Complete STEC questionnaire
• Provide hygiene advice (written if possible) and warn case that further tests are being done on the sample
• Exclude all cases until 48 hours symptom free
• If case is in risk group B consider commencing clearance once 48 hrs symptom free and exclude until GBRU in-house PCR is known or clearance achieved, whichever is sooner (Table 6)
• If case is in risk group A,C,D do not automatically exclude case, carry out risk assessment (Table 6)
• If there are symptomatic contacts arrange single diagnostic sample, give hygiene advice and exclude them until 48 hours symptom free
• Wait for GBRU in-house PCR result, available around 11 days after sample collected before starting public health actions for asymptomatic contacts in risk groups A-D (Table 7)

**Rationale**

Although the case has bloody diarrhoea, most isolates are NOT subsequently confirmed by GBRU to be viable STEC belonging to HUSEC strains. However bloody diarrhoea is more frequently associated with infection with HUSEC strains. The implementation of pragmatic precautions (exclusion while symptomatic and providing hygiene advice) and the completion of the STEC questionnaire (information about potential transmission and contacts) aims to balance the risk of transmission against imposing restrictions on the case that may not be necessary.

**Note about confirmation of STEC**

If local diagnostic laboratories do not routinely send stx PCR positive, local culture *E. coli* O157 negative samples to GBRU, HPTs are advised to agree criteria with local laboratories for sending samples to GBRU for in-house PCR and culture. Suggested criteria:

• Cases with HUS
• Cases with bloody diarrhoea (with no other obvious cause)
• Cases hospitalised with acute diarrhoeal illness
• Cases aged 5 years and under (up to 6th birthday)
• HPT has information to suggest there is a potential outbreak

**Note about hospitalisation**

Hospitalisation for acute diarrhoeal illness may be an indicator of illness severity and risk of subsequent development of HUS. However, analysis of local HPT data has not shown that a history of hospitalisation is a reliable indicator of severe STEC infection. Most cases with a history of hospitalisation are admitted for other reasons and developed diarrhoeal symptoms during the
admission or were screened as part of *C. difficile* control procedures. Analysis of national data to explore this is in progress.

**Note 9**

Local stx PCR positive, local culture *E. coli* O157 negative **no** evidence of severe illness
Where there is no evidence of severe illness:
- Define case as POSSIBLE
- If the case is aged 5 years and under it is recommended to make contact by phone with parent/guardian to confirm history and carry out a rapid risk assessment (*Appendices II*).
- Provide written information to case (or parent/guardian) and copy to the GP (*Appendices III and IV*)
- No other public health actions recommended at this stage
- Wait for GBRU in-house PCR and culture results

**Rationale**
There is a large amount of evidence showing that young children are particularly susceptible to acquiring and transmitting STEC infections and that they are also at greater risk of developing severe forms of infection eg HUS.

**Note 10**

Local stx PCR positive, local culture *E. coli* O157 negative patient reports bloody diarrhoea
If case makes contact with HPT and reports bloody diarrhoea or admission with acute diarrhoeal illness:
- Manage as a potential HUSEC strain as per **Note 8** above.
If case reports that contacts have been symptomatic
- Arrange single diagnostic sample, give hygiene advice and exclude contact until 48 hours symptom free
**Stage 2**

**Note 11**

**GBRU in-house PCR result**
- STEC isolated (STEC PCR:+, culture :) OR stx genes detected (STEC PCR:+ culture:)
  **Note 12**
  Define as CONFIRMED case

- **Stx2 & eae (positive)**
  **Note 13**

- **STEC isolated**
  **Note 14**

- **HPT has already begun public health actions?**
  **Note 15**

1. **All cases:** reinforce hygiene advice, complete STEC questionnaire if not already done, seek evidence of transmission
2. **HUS/probable E. coli O157:**
   - All actions as per STEC O157 management (should have been completed/in progress)
3. **Bloody diarrhoea:**
   - Case in risk group A,C,D initiate clearance samples
4. **Risk group B (regardless of bloody diarrhoea):**
   - Continue clearance samples and continue exclusion until cleared

- **Is there evidence of transmission?**
  **Note 7**

  - No further public health action required with contacts
  - Review both case and contacts and route of transmission

- **Is there evidence of transmission or case aged 5 years and under?**
  **Note 17**

  - Exclude until 48 hours symptom free
  - Case in risk group initiate clearance samples
  - Exclude asymptomatic contacts in risk group B ONLY
  - Manage symptomatic contacts as ‘probable’ cases and complete STEC questionnaire

- **Go to Stage 3**

**Wait for GBRU stx subtyping information usually available about 16 days after initial frontline laboratory report to HPT or 21 days after original sample taken**
Stage 2

Note 11

Detection of stx and eae genes in a specimen does not indicate the viability of the organism. It is the combination of both stx and eae gene profile and culture result from GBRU which is most useful in directing public health actions. In stage 2, the possession of stx2 and eae is used to identify infections caused by potential HUSEC strains.

Note 12

GBRU in-house PCR results

At this stage the GBRU in-house PCR results are reported on GDW and include the stx and eae results (Appendix I):

- STEC isolated (STEC PCR:+ culture:+) – this indicates that STEC is present and viable and an isolate is available for WGS.
- STX genes detected (STEC PCR:+ culture:- ) – this indicates that STEC is present but the negative culture indicates that the organism is not viable or the numbers are too low to isolate
- STEC NOT isolated (STEC PCR:- culture:- ) – this indicates that STEC is not present. It is important to note that between 30 to 40% of stx PCR positive results are not confirmed by GBRU, which may be due to a variety of reasons which include:
  - DNA degrades quickly in faecal samples, the inherent turn-around time between local lab testing and GBRU testing can affect detection.
  - Local diagnostic laboratories perform direct DNA extraction from the sample, whereas GBRU does an overnight broth enrichment step. If the bacteria are viable and multiply the enrichment step increases the amount of DNA present, if the bacteria are dead enrichment actually dilutes the DNA.
  - Pathogens are not evenly distributed throughout a faecal sample
  - Commercial PCR assays may be more sensitive than the GBRU PCR assay. There has not been a direct comparison of performance.

Note on PCR results

Be aware that the PCR result is from DNA extracted from a faecal sample. The combination of positive stx1/stx2/eae genes may be derived from more than one strain of STEC and non-STEC pathogens in that sample.

Note 13

Stx2 positive and eae positive (may also be stx1 positive)

- For all combinations of stx and eae results, change case definition to CONFIRMED
- If the result is positive for both stx2 and eae regardless of stx1 go to the next question in the algorithm
- For all other combinations of stx and eae there are no public health actions beyond ensuring case is excluded until 48 hours symptom free.
Note 14

STEC isolated
- If STEC is not isolated there are no public health actions usually recommended beyond ensuring case is excluded until 48 hours symptom free.
- If STEC is isolated the organism is viable and because it possesses genes for stx2a and eae it is also a potential HUSEC strain.
- If the result is positive for both stx2 and eae regardless of stx1 and organism is viable go to the next question in the algorithm.

Note 15

Case is already known to HPT and public health actions have been commenced
For cases with a history of HUS or probable E. coli O157 full public health actions are likely to have begun and may have been completed prior to the GBRU PCR result. If there is a history of bloody diarrhoea some public health actions are likely to have begun particularly if the case is in a risk group.
ALL cases:
- Change case definition to CONFIRMED
- Re-assess evidence of transmission. Potentially a further incubation period has passed since initial contact with the case
HUS/probable E. coli O157:
- All actions as per STEC O157 management should have been completed or are in progress, including providing advice and the possible exclusion and screening of contacts (Table 7)
Cases with bloody diarrhoea:
- Review public health actions, including providing advice and the possible exclusion and screening of:
  - asymptomatic contacts in risk groups A,C,D (Note 8) (Table 7)
  - symptomatic contacts (Table 7)
Children < 6yrs of age (risk group B) regardless of symptoms:
- If already excluded continue until clearance has been achieved
- If NOT already excluded carry out risk assessment to determine need for exclusion until clearance has been achieved (Table 6). However if there is evidence of transmission exclude until cleared.

Rationale
The STEC is viable and a potential HUSEC strain. It may not have produced serious symptoms in this case, but if the case is shedding there is still the potential for transmission particularly if the case is a young child. Some strains appear to cause more severe disease in secondary cases.
**Note 16**

**Public health actions not started**
If the HPT was not previously aware of the case, but identified it from GDW or from initial clinical history the case had been assessed to be low risk:
- Case is defined as CONFIRMED
- Complete the STEC questionnaire if not already done
- Re-inforce hygiene advice that may have been provided to the case in the letter/leaflet
- Assess for evidence of transmission
  - if there is NO evidence of transmission exclude case until 48 hours symptom free, but there are no further public health actions for the case or their contacts
  - if there is evidence of transmission then follow up is recommended.

**Rationale**
This case is infected with a potential HUSEC strain (serogroup/serotype and stx2 subtype not yet known). An assessment of potential transmissibility is advised, even though the strain has not caused severe illness in this case.

**Note 17**

**There is evidence of transmission or the case is aged 5 years and under and infected with potential HUSEC strain**
- If case is in risk group B carry out risk assessment to determine need for exclusion until clearance has been achieved (Table 6). However if there is evidence of transmission exclude until cleared.
- If case is in risk group A,C,D carry out risk assessment to determine need for exclusion until clearance has been achieved (Table 6)
- Asymptomatic contacts in risk group B, exclude until the screening has been completed (Table 7)
- Asymptomatic contacts in risk group A,C,D screening not recommended (Table 7)
- Symptomatic contacts
  - manage as a PROBABLE case
  - arrange single diagnostic specimen and exclude until 48 hours symptom free
  - if symptomatic contact is in risk group A-D continue to exclude until the diagnostic/screening result is known (Table 7)

**Rationale**
Children aged 5 years and under can shed STEC for prolonged periods and onwards transmission is not uncommon and if a case has symptomatic contacts assume that transmission may have occurred.
No HPT has already begun public health actions?

Yes

STEC belongs to a HUSEC strain?

Note 19

No

Has GBRU advised that serotype has other markers eg aggR or is a serotype of concern?

Yes

Is case aged 5 years and under?

No

No further PH action required

Yes

Check that all PH actions have been completed

Update risk assessment

Has GBRU advised that serotype has other markers eg aggR or is a serotype of concern?

No

Is there evidence of transmission?

Yes

Complete STEC questionnaire

Reinforce hygiene advice

No

Is case aged 5 years and under?

Yes

Exclude until 48 hours symptom free

Risk assess both case and contacts and route of transmission

Consider seeking expert opinion to decide proportionate screening/clearance AND exclusion strategy

No

STEC belongs to a HUSEC strain?

Note 19

Note 20

No

Yes

HPT has already begun public health actions?

Note 21

Note 24

No

Yes

Evidence of transmission or case aged 5 years and under?

Note 22

Note 23

Note 18

Define as CONFERMED case

Note 19

Note 20

Note 21

Note 24

Note 22

Note 23

Note 25

Note 26

Note 18

Note 19

Note 20

Note 21

Note 24

Note 22

Note 23

Note 25

Note 26

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Stage 3

Note 18

GBRU WGS results

- Define case as CONFIRMED (if case not previously reported)

The stx subtypes stx2a/stx2c/stx2d are strongly associated with risk of HUS, particularly if positive for eae or aggR gene. Currently aggR is not routinely reported on GDW. From the preliminary analysis of the national data, approximately 14% of isolates with stx2a/2c/2d are eae negative. The proportion of these that were aggR is not known.

Note 19

Serotype has the stx subtype stx2a/2c/2d (HUSEC strain)

- It is recommended that all isolates with stx2a/2c/2d regardless of eae, should be followed up for public health action.
- GBRU can provide the aggR result on a case by case basis.

Note 20

Serotype has a non HUSEC strain profile

Bacteria are constantly evolving and there have been documented instances when an E. coli strain of low pathogenicity has acquired stx genes eg STEC O26:H11 (stx1a, eae) acquired stx2a genes to become (stx1a, stx2a, eae) which significantly increased pathogenicity or EAEC O104:H4 (aggR) which also acquired stx2a genes and became (stx2a, aggR) causing a Europe wide outbreak with a high proportion of HUS cases in adults.

It is probable that other strains will emerge and GBRU will alert HPTs.

Note 21

Serotype has the stx subtype stx2a/2c/2d (HUSEC strain) and the HPT has commenced public health actions

If the strain has the stx subtype stx2a/2c/2d (HUSEC strain) and the STEC questionnaire has already been completed:

- For cases with HUS / bloody diarrhoea / probable O157 STEC public health actions will probably have been completed
  - Check that all public health actions have been completed.
- For cases in risk groups it is possible that there may be some outstanding public health actions particularly if the initial GBRU result in Stage 2 was stx2 but negative for eae.
  - Review public health actions already completed and complete STEC questionnaire if not already done
  - Review risk assessment. Seek advice from NIS about aggR status and the risk presented by the serotype, consider the time period since original sample was submitted/disease onset date.
- For all other cases there are no further public health actions.
Note 22

Case in risk group B or there is evidence of transmission
If there is evidence of transmission or the case is in risk group B:
- Review all public health actions to ensure that they have been completed
- If no evidence of transmission close case.

Note 23

Case not in risk group B and no evidence of transmission
- If there is NO evidence of transmission and the case is not in risk group there are no further public health actions
- If the case is in risk group A,C,D follow guidance in Table 6

Note 24

Serotype has the stx subtype stx2a/2c/2d (HUSEC strain) and the HPT has not begun public health response
For all cases:
- Complete the STEC questionnaire
- Reinforce hygiene advice verbally and in writing
If there is evidence of transmission:
- Exclude case and symptomatic contacts until 48 hours symptom free
- Complete risk assessment for case and symptomatic contacts and potential route of transmission
- Consider obtaining expert opinion from NIS taking into account the risk presented by the serotype, the time period since original sample was submitted/disease onset date, and risk assessment information for both case and symptomatic contacts to determine if further public health actions are recommended.

Note 25

There is evidence of transmission
- Exclude case and symptomatic contacts until 48 hours symptom free
- Complete risk assessment for case and symptomatic contacts and potential route of transmission
- Consider obtaining expert opinion from NIS taking into account the risk presented by the serotype, the time period since original sample was submitted/disease onset date, and risk assessment information for both case and symptomatic contacts to determine if further public health actions are recommended.

Note 26

Risk group B and no evidence of transmission
- Exclude case and symptomatic contacts until 48 hours symptom free
- Complete risk assessment for case and contacts and route of transmission
- Seek advice from NIS taking into account the risk presented by the serotype, the time period since sample was submitted/disease onset date, and risk assessment information for both case and symptomatic contacts; to determine if further public health actions are advisable.