Enteropathogenic *Escherichia coli* Outbreak and its Incubation Period: Is it Short or Long?

Dong-Woo Lee a,*, Jin Gwack b, Seun-Ki Youn b

aDivision of Public Health Crisis Responses, Korea Centers for Disease Control and Prevention, Osong, Korea.
bDivision of Epidemic Intelligence Service, Korea Centers for Disease Control and Prevention, Osong, Korea.

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Abstract

Objectives: The aim of this study is to determine the incubation period of enteropathogenic *Escherichia coli* (EPEC), which creates several outbreaks in a year in South Korea.

Methods: We reviewed all water and food-borne outbreaks data reported to the Korea Centers for Disease Control and Prevention (KCDC) from 2009 to 2010 and determined their characteristics. Through this process, we can presume the incubation period of EPEC among outbreaks in South Korea.

Results: A total of 497 water and food-borne outbreaks were reported to KCDC and 66 (13.28%) are defined as *E coli*-origin outbreaks. EPEC was the most common subtype of *E coli*, being confirmed as a causative organism in 26 outbreaks. Overall attack rate was 15.85% (range 0.9–100). The subjects were eight outbreaks that have a clear history of single exposure and we can estimate the incubation time of EPEC as minimum 0.5 hours to maximum 34.0 hours with a mean 12.9 hours (range 4.5–24.0). The cases of those cannot completely rule out the chance of multiple exposure from same source or place have minimum 1.0 hour, to a maximum of 195.5 hours and a mean 30.5 (range 22.7–61.0) hours of incubation period.

Conclusions: This serial analysis suggests that EPEC has actually shorter mean incubation period as much as 12 hours. When this period is longer than 1 day or over, then the epidemiologic investigator should consider the chance of repeated or continuous exposure by making it clear whether there is any chance of any other exposure in common.

1. Introduction

*Escherichia coli* is the predominant nonpathogenic facultative flora of the human intestine. Most people normally carry harmless strains of *E coli* in their intestine. Both the harmless strains and those that cause diarrhea are acquired primarily through ingestion of contaminated food or water [1]. Person-to-person and animal-to-human transmission is through the oral-fecal route. However, several strains of *E coli* have usually
caused diarrhea/gastroenteritis in human which settles within several days without specific treatment [2].

The varieties of *E coli* can be grouped into six pathotypes according to their virulence determinants whose specific nature makes each pathotype different both clinically and epidemiologically: enteropathogenic (*EPEC*), enterohemorrhagic (*EHEC*), enteroinvasive (*EIEC*), enterotoxigenic (*ETEC*), enteraggregative (*EAEC*), and diffuse adherent (*DAEC*) [3].

*EPEC* is one of the oldest recognized diarrheagenic *E coli*. *EPEC* cause either a watery or bloody diarrhea [2]. *EPEC* has been well known to be highly related to infant diarrhea in developing countries through the pioneering work of Bray [4] who established the importance of *EPEC* as a cause of outbreaks of infantile gastroenteritis in the UK in the 1940s. These continued until the early 1970s, but since then outbreaks caused by ‘classical’ *EPEC* strains have become very rare [5]. Infections caused by *EPEC* are difficult to differentiate from those with other causes; symptoms include watery diarrhea, sometimes accompanied by low-grade fever and vomiting. However, *EPEC* infection may be severe, vomiting may make oral rehydration difficult and life-threatening dehydration may ensue. Furthermore, disease caused by *EPEC* may be protracted, resulting in weight loss, malnutrition, and death [6]. Its characteristics are relatively well defined. However, there are some controversies about the incubation period both it can be as short as 6 hours or can be as long as 6 to 10 days [7,8]. As a result, it is known that *EPEC* has just ‘variable’ incubation time [9].

In South Korea, all outbreaks by water-borne and food-borne disease with two or more persons should be reported to a local public health center for epidemic investigation. When there is an outbreak of which source infectious agent is thought as *EPEC*, Korea Centers for Disease Control and Prevention (KCDC) epidemic intelligence service (EIS) officers estimate the causal relationship between exposure and onset of outbreak in consideration of two factors, laboratory result and epidemiologic nature, especially during the incubation period. Following the WHO guideline, KCDC has suggested the incubation period of *EPEC* as 1 to 6 days [10,11]. Nevertheless, it has caused some difficulties in presuming first exposure time during epidemic investigations when *EPEC* was confirmed as causative organism by laboratory result, but incubation period of the epidemic was very short, e.g., less than 6 hours.

This study is dedicated to clarifying whether the incubation period of *EPEC* is truly long over 1 day or whether it is shorter than several hours by analyzing recent *EPEC* outbreaks in South Korea.

2. Methods

The incubation period, which is the amount of time between infection with a virus or bacteria and the start of symptoms, can vary from one case to another according to the route by which the person was exposed, the dose of bacteria received, and other factors, including immune status. Estimates of the incubation period are further complicated by the fact that some patients have had opportunities for multiple exposures to the pathogens. The particular exposure that caused disease may prove impossible to determine [10].

For these reasons, the most reliable estimates of the incubation period are based on a study of cases having a single documented exposure to a known case. We reviewed all water and food-borne outbreaks data reported to KCDC from 2009 to 2010 and determined whether these outbreaks were truly defined vehicles of transmission and single exposure. With this process, we can presume the incubation period of *EPEC* among outbreaks in South Korea during 2009–2010.

3. Results

From January 1, 2009, to December 31, 2010, a total of 497 water and food-borne outbreaks were investigated and reported to KCDC and 66 (13.3%) were defined as *E coli*-origin outbreaks. The distribution of subtype is shown in Table 1. *EPEC* was the most common subtype of *E coli*, being confirmed as a causative organism in 26 outbreaks, followed by 20 of *ETEC*, seven of *EHEC*, five of *EAEC*, and eight of mutual or other subtypes.

*EPEC* outbreaks had, as a whole, 11,302 population at risk and 1791 cases were defined as *EPEC* related cases. Its overall attack rate was 15.9% (range 0.9–100.0). This wide range of attack rate mainly comes from the variety of outbreaks; from an outbreak of small group less than five, but all are defined cases to that of group food service in a school over 1,000 students but had small cases.

Among these 26 outbreaks, to presume a more precise incubation period of *EPEC*, we selected 13 outbreaks that had an obvious identified single-point

| Table 1. *E coli* subtypes of outbreaks: Korea, 2009–2010 |
|---------------------------------------------------------|
| Subtypes       | Cases | Percentage |
|----------------|-------|------------|
| EPEC           | 26    | 39.4%      |
| ETEC           | 20    | 30.3%      |
| EHEC           | 7     | 10.6%      |
| EAEC           | 5     | 7.6%       |
| Unspecified    | 8     | 12.1%      |
| Total          | 66    | 13.3%*     |

*Total cases and percentages of *E coli* origin outbreaks in Korea, 2009–2010 except *.

*means incidence rate of *E coli* outbreaks among all water and food-borne outbreaks in Korea, 2009–2010.
exposure history and which had accurate time interval information from exposure to first symptom onset. Of the 13 outbreaks, eight have a clear history and the defined cases had only one meal in common, before and after of possible exposure time. Meanwhile, five have a chance of continuous exposure despite of their assumed single exposure time by epidemiologic investigation. These were students in school who had lunch or dinner from the same ‘group food catering service’ at the same place, in every day.

From the outbreaks that had no possibility of repeated or continuous exposure, we can estimate the incubation period of EPEC as shown in Table 2. Minimum incubation period (MiIP) is 0.5 hour, maximum incubation period (MaIP) is 34.0 hours, and mean incubation period (MIP) is 12.87 (range 4.5—24.0) hours. However, the cases that cannot completely rule out the chance of multiple exposure from same source or place (Table 3), MiIP is 1.0 hour, MaIP is 195.5 hours, and MIP is 30.5 (range 22.7—61.0) hours.

Frequencies of clinical symptoms among cases are shown in Table 4. The most common symptom was diarrhea, followed by abdominal pain.

4. Discussion

In 2010, EPEC was one of the three most common causative organisms of water- and food-borne outbreaks in Korea, next to norovirus and salmonella. When an outbreak has occurred, sophisticated epidemiologic investigation is important to determine the source of infection, the exact pathogen, and how it is transmitted through the persons. Prompt and exact response upon investigation is crucial to prevent spread of disease to local community. In this process, to identify correct pathogen is a key point to layout a whole outbreak. However, laboratory results are not the only concern when determining the cause; epidemiologic characteristics should always be considered together.

Appropriate standards or guidelines for epidemiologic features of certain pathogens are important when the field outbreak investigation begins. Incubation period is a core-determining factor in these guidelines for inferring the causative organism of outbreak with epidemic curve. Nevertheless, the incubation period of EPEC is not well established in guidelines, including that of KCDC. The WHO guideline states that the EPEC incubation period is 1—6 days (as short as 12—36 hours) [10]. However, it is just ‘variable’ in the guideline of CDC [9]. Moreover, in the past reports, Nakamura and colleagues said it can be as long as two to 20 days, though it can be chiefly 1—5 days [7]. However, in Korea, when there is an EPEC outbreak, it is often as short as 6 hours or less.

Our results suggest that MIP of EPEC is not just ‘variable’. ‘Outbreak with clear single exposure history’
means outbreak occurred among persons who had only
one meal together and had no other chance of common
exposure before and after suspected event. MIP of EPEC
outbreaks in this setting is only 12.9 hours. It is shorter
than 1 day. With this trait, outbreaks of EPEC should
show a different epidemic curve from that of the nor-
ovirus, which usually presents a flatter curvature.

MIP of Outbreaks of ‘group catering service’ in
school, however, is three times longer as 32 hours and
MaIP extends up to 195 hours, which is about 8 days. In
this situation, persons in school (including teachers and
other workers) had same meals in the same place in
every day. There was higher chance of repeated or
continuous exposure for EPEC. As a result, without
subgroup analysis considering characteristics of expo-
sure, intermingled incubation period of EPEC outbreaks
looks much longer and widely dispersed.

Recent studies have suggested, however, EPEC is
not a homogeneous pathogen. ‘Typical’ EPEC carries
adherence factor plasmid (pEAF). This plasmid encodes
bundle-forming pili (BFP), which promote bacterial
adherence to epithelial cells and are an essential viru-
ulence determinant [12] and a transcriptional activator
(PER), that upregulates genes within a chromosomal
pathogenicity island [13,14]. This pathogenicity island
is thought to encode a number of essential virulence
proteins, including the surface protein intimin (the
product of the eae gene), which is required to produce
the attaching-effacing lesions that are a key feature of
EPEC-induced pathology [15]. A subset of EPEC,
known as ‘atypical’ EPEC, does not carry pEAF and
hence does not produce BFP or PER [16]. Accordingly,
their role in the disease is controversial. However, there
are several reports that ‘atypical’ EPEC show different
clinical aspects; Nguyen and colleagues suggested that
atypical EPEC is associated with prolonged diarrhea in
children [15].

In this study, we did not collect data about specific
type of EPEC in each outbreak. Therefore, we cannot
infer relationship between the length of incubation
period and each type of EPEC. However, KCDC is
planning further study and will be combining epidemi-
ologic investigation and specific laboratory process
about typing matches to determine whether certain
outbreaks are from ‘typical’ or ‘atypical’ EPEC.
5. Conclusion

The clinical and other epidemiologic characteristics of EPEC are well known. However, its incubation period is not well-established in guidelines for epidemiologic investigation. We estimated roughly the incubation period of EPEC with limited data in 2 years for 2009 and 2010. Nevertheless, this serial analysis suggests that EPEC has a relatively shorter incubation period, i.e., as much as about 12 hours. When this period is 1 day or more, then EIS officer should consider the chance of repeated or continuous exposure and focus his or her investigation on determining whether the cases truly have a single-point exposure. It has not yet been discovered whether this difference comes from the type of EPEC (typical vs. atypical), so further investigation through laboratory support should be performed in the near future.

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