Evaluation of the Surveillance of Hemolytic Uremic Syndrome in British Columbia

Should It Remain Reportable?

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ABSTRACT

Background: Hemolytic Uremic Syndrome (HUS) was made reportable in British Columbia (BC) in 1998 to detect, control and prevent verotoxigenic *Escherichia coli* (VTEC) cases. Concerns about under-reporting of HUS cases triggered the assessment of the sensitivity and timeliness of the reporting process in order to guide recommendations around reportability of this syndrome in BC.

Methods: The BC hospitalization database was used to estimate the total number of HUS cases from April 30, 1998 to December 31, 2005. HUS and VTEC cases reported in the integrated Public Health Information System (iPHIS), and HUS cases reported by a surveillance form were linked to hospitalized cases. The proportion of HUS cases detected by each of the surveillance processes was assessed. The time interval between onset of diarrhea and reporting of HUS and VTEC cases to the BC Centre for Disease Control was compared.

Results: 57 HUS cases were hospitalized. Sensitivity of reporting through the surveillance form and through iPHIS was 7.0% and 19.3%, respectively. The median time interval between onset of diarrhea and reporting of both HUS and VTEC cases to iPHIS was seven days. The median time interval for reporting HUS cases via the surveillance form was 25 days.

Conclusions: HUS cases were severely under-reported, the timeliness of reporting of these cases had no advantage when compared to the reporting of VTEC cases, and no public health action aimed at reducing the transmission of VTEC infections resulted from this surveillance system. The reportability of HUS in BC needs to be reconsidered, or its surveillance considerably improved.

Key words: Hemolytic uremic syndrome; surveillance; quantitative evaluation; sensitivity

Hemolytic Uremic Syndrome (HUS) is a clinical syndrome characterized by acute renal failure, hemolytic anemia, and thrombocytopenia.¹ HUS mainly affects infants and young children²⁻⁴ and is a major cause of acute renal failure in children worldwide.⁵ The mortality rate among children afflicted by HUS varies between 3-5%,⁶ and about 25% of HUS cases have long-term renal sequelae.⁷ HUS usually occurs within days of an enteric infection, but in rare cases, it can follow other infections or be due to genetic deficiencies.⁸ HUS is most often secondary to a verotoxigenic *Escherichia coli* infection (VTEC).^{2,5} *E. coli* serotypes O157:H7 and O157:non motile are the most common VTEC identified in North America and Europe and are the most likely to cause HUS.² Three to eight percent of *E. coli* O157:H7 infections progress to HUS.⁹

In the province of British Columbia (BC), an average of 4.0 VTEC cases per 100,000 population (161 cases) are reported each year (1996-2005), which is comparable to the Canadian average incidence rate (4.5 cases per 100,000 population per year; 1996-2005).¹⁰

In BC, post-diarrheal HUS defined by a standardized case definition (<http://0-www.cdc.gov.mill1.sjlibrary.org/epo/dphsi/casedef/hemolyticcurrent.htm>, Accessed: October 2007) was made reportable in 1998 to: increase the detection of cases of infection with VTEC; improve the timeliness of reporting of these cases; improve secondary VTEC infection case finding; and reduce the transmission of this pathogen. BC physicians were mandated to report cases to their Health Authority (HA), which in turn report them to the BC Centre for Disease Control (BCCDC) through an enhanced surveillance fax form (to increase timeliness) and through the BC integrated Public Health Information System (iPHIS). This electronic system collects information reported by HA on cases of notifiable diseases and is not accessible at the hospital level.

Concerns about under-reporting of post-diarrheal HUS (hereby referred to as HUS) cases and lack of public health actions aimed at reducing the burden of VTEC infections through the detection of HUS cases triggered the evaluation of the surveillance of this syndrome in BC. The objective of our study was to describe the

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epidemiology of HUS between April 30, 1998 and December 31, 2005 and assess the sensitivity and timeliness of reporting methods in order to guide recommendations around reportability and surveillance of this syndrome in BC.

METHODS

The US Centers for Disease Control and Prevention's guidelines for evaluating surveillance systems were used.¹¹ We assumed that cases diagnosed with HUS would be hospitalized.^{2,12} The BC hospitalization database was used to estimate the total number of cases of HUS. A HUS case was defined as a BC resident who was hospitalized with a diagnostic code of HUS (ICD-9-CM 283.11 or ICD-10 D59.3) plus any other diagnostic code related to *E. coli* (ICD-10 A04.3) or other bacterial food poisoning infections (ICD-10 A05.9; ICD-9 005) between April 30, 1998 (date when HUS was made reportable) and December 31, 2005.

Data on HUS and VTEC cases reported in *iPHIS* during the study period were extracted for all HA. HUS surveillance fax forms, archived at the BCCDC, were reviewed. The 2001 BC census was used to estimate the population by age groups and by HA.¹³

Age, sex, HA, and date of admission were used to link hospitalized cases with HUS and VTEC cases reported in *iPHIS*, and with HUS cases reported by the fax form. Cases' names and dates of birth were used to link VTEC cases with HUS cases reported in *iPHIS*.

Age and sex distribution, length of hospital stay, and mortality of HUS cases were described. Average annual incidence rates were calculated by age group. Sensitivity was assessed by calculating the proportion of hospitalized HUS cases reported by the surveillance form, and in *iPHIS*. Sensitivity was calculated for all ages and for children less than 16 years. Timeliness was assessed by evaluating the time interval between onset of diarrhea and reporting of HUS, as well as the time interval between hospital admission and reporting of HUS. Timeliness was compared between the two reporting processes. Timeliness was also assessed for HUS cases that had VTEC concomitantly reported in *iPHIS*. For these cases, the time interval between onset

Figure 1. Cases and incidence rates of hospitalized HUS cases, British Columbia, April 30, 1998 to December 31, 2005

* incomplete year

of diarrhea and reporting of VTEC, and the time interval between hospital admission and reporting of VTEC were evaluated.

Fisher's exact test was used to calculate 95% confidence intervals for proportions. Microsoft® Office Excel 2003 was used for data management. Descriptive analyses were done using SPSS® 14.0 (2005) for Windows software.

This study was part of a program evaluation and did not require ethical approval.

RESULTS

Between April 30, 1998 and December 31, 2005, 57 cases (0.18 per 100,000 population annually) of HUS were hospitalized in BC. The number of cases per year (excluding 1998) ranged from 4 to 13 (Figure 1). The age of cases ranged from 1 to 86 years (median: 7.0) (Table I), and the highest incidence rate was observed among children less than 5 years (average of 1.52 per 100,000 population annually). Males were predominant overall (54.4%), although females were predominant among the less than 16 year age group (57.1%). Most cases (77.2%) were hospitalized for more than four days and the median stay was eight days (range: 1-180 days). Three cases (5.3%) died while hospitalized. These cases were 9, 39, and 77 years old when they died.

Four HUS cases were reported via the fax form and 14 were reported in *iPHIS*. All HUS cases reported via the fax form

were also reported in *iPHIS* and could be linked to cases in the hospitalization database. Three of the 14 HUS cases reported through *iPHIS* could not be linked to cases in the hospitalization database: 1 case did not meet the case definition and 2 could not be found in the hospitalization database because information on them was insufficient. Among HUS cases reported in *iPHIS*, 10 (71.4%) had a VTEC infection concomitantly reported in the system.

The sensitivity of reporting through *iPHIS* was 19.3% (95% CI: 10.0-31.9) compared to 7.0% (95% CI: 1.9-17.0) through the fax form (Table II). Sensitivity of reporting was slightly higher for children less than 16 years. All cases reported through the fax forms and 9 cases (82%) reported in *iPHIS* were from the same HA.

It took a median time of seven days after onset of diarrhea to report HUS and VTEC cases to *iPHIS*, and less than a week after admission to hospital (Table III). It took a median time of three weeks after either onset of diarrhea or admission to hospital for HA to fax HUS forms to the BCCDC.

DISCUSSION

We described the epidemiology and reporting of HUS in British Columbia between April 30, 1998 and December 31, 2005. Children less than five years old had the highest incidence rate. This is similar to previous studies²⁻⁴ and illustrates the

TABLE I

Characteristics of Hospitalized HUS Cases, British Columbia, April 30, 1998 to December 31, 2005

Characteristics	HUS Cases – All (N=57)	HUS Cases Less than 16 Years (n=42)
Age (y)	n (mean annual incidence/100,000)	n (mean annual incidence/100,000)
0-4	24 (1.52)	42 (0.72)
5-15	18 (0.42)	
16-64	8 (0.04)	
65+	7 (0.17)	
All	range: 1-86 mean: 19.5 median: 7.0	range: 1-13 mean: 5.3 median: 4.0
Gender	n (%)	n (%)
Female	26 (45.6)	24 (57.1)
Male	31 (54.4)	18 (42.9)
Outcome	n (%)	n (%)
Dead	3 (5.3)	1 (2.4)
Hospital stay (days)	n (%)	n (%)
>4	44 (77.2)	35 (83.3)
1-4	13 (22.8)	7 (16.7)
	range: 1-180 mean: 15.0 median: 8.0	range: 1-49 mean: 11.5 median: 8.5

TABLE II

Sensitivity and 95% Confidence Interval (CI) of Reporting Routes of Post-diarrheal HUS Cases, British Columbia, April 30, 1998 to December 31, 2005

Reporting Route	All Cases	Sensitivity Children <16 Years
iPHIS (N=14)	19.3% (11/57) CI [10.0-31.9]	26.2% (11/42) CI [13.9-42.0]
Fax forms (N=4)	7.0% (4/57) CI [1.9-17.0]	9.5% (4/42) CI [2.7-22.6]

TABLE III

Time (Days) between Onset of Diarrhea or Admission to Hospital and Reporting of HUS and VTEC to the British Columbia Centre for Disease Control, British Columbia, April 30, 1998 to December 31, 2005

Reporting Route (Health Event)	Onset of Diarrhea	Admission to Hospital
Fax form (HUS) (N=4)	Range: 14-57 Median: 25.0	Range: 9-54 Median: 21.0
iPHIS (HUS) (N=14)	Range: 5-35 Median: 7.0	Range: 1-33 Median: 2.5
iPHIS (VTEC) (N=10)	Range: 4-11 Median: 7.0	Range: 1-7 Median: 3.0

importance of HUS in this vulnerable population. The incidence rate in children less than 16 years old (0.72/100,000) is lower than what has been reported in Canadian children of the same age (1.11/100,000).¹ The mortality rate in this age group (2.4%) is also lower than the Canadian rate for children of the same age, but similar to children in other industrialized countries (1.4-2.7%).^{1,2,14} However, small numbers, the fact that some cases may have died after discharge or during a subsequent hospitalization, and differences in methodology probably underestimate incidence and mortality rates.

Our results revealed that HUS was severely under-reported in BC, with at best one case out of four detected through the surveillance processes. Reporting of HUS cases with the fax form was ineffective: only four cases were reported during the study period, and these cases were already reported in iPHIS. Although it is believed that

this condition is under-reported in North America, our sensitivity results were remarkably lower than those from studies conducted in California and New York, where 44-65% of hospitalized cases were reported to the public health surveillance systems.^{2,3} The reason for this difference is unclear.

After the study was done, a qualitative survey was conducted with BC HA to better interpret results. Breaks in the reporting system might explain the low sensitivity. First, there is no clear procedure for hospitals to report HUS to HA (and some HA mentioned that their local hospital most likely would not report HUS cases to them). In addition, most HA were not aware that HUS cases should be immediately reported to the BCCDC using a fax form. Moreover, when a HUS case is known to be infected with VTEC, most HA report only the VTEC infection.

When HUS surveillance was implemented in BC, the fax form was expected to be

the fastest way by which the condition would be reported to the BCCDC. Results revealed that this reporting route was less timely than the reporting of both HUS and VTEC through iPHIS.

Since 1991, the BCCDC Laboratory Services have the capacity to identify verotoxins in stools and to isolate O157 and non O157 VTEC strains (personal communication with Ana Paccagnella, BCCDC, January 2007). Local laboratories culture stools selectively for *E. coli* O157 and then send the isolate to the BCCDC Laboratory Services for further testing. In addition, bloody stool samples are submitted directly to the BCCDC Laboratory Services where they are tested for verotoxins and cultured for *E. coli* O157 and non-O157. When a VTEC is detected, further tests are conducted (serotyping and Pulsed Field Gel Electrophoresis) to identify the strain. In addition to being reported in iPHIS, VTEC cases are electronically reported to BCCDC Epidemiology Services via an in-house system. During the study period, VTEC surveillance led to the detection of clusters and outbreaks (that included HUS cases) for which a source was confirmed and public health measures implemented (BCCDC Epidemiology Services archives). However, no VTEC clusters or outbreaks were detected at a provincial level via HUS surveillance during the same period.

The objectives for which HUS was made reportable were not met by the surveillance system. HUS cases were critically under-reported, the timeliness of reporting of these cases had no advantage when compared to the reporting of VTEC cases, and no public health actions aimed at reducing the transmission of VTEC infection resulted from this surveillance system. In contrast, VTEC surveillance succeeded in detecting outbreaks and in reducing the transmission of this pathogen by the implementation of control measures in affected communities.

Two options should be considered regarding the surveillance of HUS in BC: reconsider its reportability, or significantly improve its surveillance. If this syndrome is removed from the BC reportable communicable diseases list, the BCCDC will need to ensure that its laboratory receives all bloody stool specimens and *E. coli* O157 isolates from every HA, and that VTEC

surveillance is maintained. Alternatively, if HUS remains reportable, HA will need to ensure that cases are being systematically reported locally and provincially. In either case, reporting through the fax form should be abolished since it offered no advantage.

The time interval between onset of diarrhea and reporting of HUS might have been affected by factors such as clinical presentation and access to health care. These factors are not directly related to the timeliness of the surveillance system, but could have biased its measure.

Our evaluation was conducted at the provincial level; it did not assess the sensitivity and timeliness of reporting of HUS cases at the HA level. Regional considerations should be taken into account before deciding if HUS remains reportable.

To ensure specificity in our case definition, we eliminated one HUS case reported in iPHIS. Including this case would have slightly increased the sensitivity of reporting of HUS cases, but even then this result would have remained of concern.

To our knowledge, it is the first time that the evaluation of the surveillance of HUS has been conducted in Canada. Our findings provide science-based evidence to guide reportability of HUS in British Columbia. This type of assessment is a useful tool applicable to other conditions in Canada and globally in order to ensure that surveillance remains efficient and leads to public health action.

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RÉSUMÉ

Contexte : Afin de détecter, de traiter et de prévenir les cas d'infection à *E. coli* producteur de vérotoxine (ECPV), la Colombie-Britannique a rendu obligatoire la déclaration du syndrome hémolytique urémique (SHU) en 1998. Par crainte que les cas de SHU soient sous-déclarés, il a été décidé d'évaluer la sensibilité et l'opportunité du processus de notification en vue de formuler des recommandations sur la déclaration du syndrome dans la province.

Méthode : D'après la base de données des hospitalisations de la C.-B., nous avons estimé le nombre total de cas de SHU survenus entre le 30 avril 1998 et le 31 décembre 2005. Les cas de SHU et d'ECPV déclarés dans le système intégré d'information sur la santé publique (SIISP) et les cas de SHU déclarés sur des fiches de surveillance ont été reliés aux cas hospitalisés. Nous avons calculé la proportion des cas de SHU détectés par chacun des processus de surveillance. Nous avons ensuite comparé l'intervalle entre l'apparition d'une diarrhée et la déclaration des cas de SHU et d'ECPV au BC Centre for Disease Control.

Résultats : Cinquante-sept cas de SHU ont été hospitalisés. La sensibilité des déclarations sur les fiches de surveillance et dans le SIISP était de 7 % et de 19,3 %, respectivement. L'intervalle médian entre l'apparition de la diarrhée et la déclaration des cas de SHU et d'ECPV au SIISP était de sept jours. L'intervalle médian de déclaration des cas de SHU sur les fiches de surveillance était de 25 jours.

Conclusion : Les cas de SHU étaient fortement sous-déclarés, la déclaration des cas de SHU était beaucoup moins rapide que pour les cas d'ECPV, et le système de surveillance du SHU n'a entraîné aucune mesure de santé publique visant à réduire la transmission des infections à ECPV. Il faudrait soit revoir la pertinence de déclarer les cas de SHU en C.-B., soit améliorer considérablement le système de surveillance du syndrome.

Mots clés : syndrome hémolytique urémique; surveillance; évaluation quantitative; sensibilité