Case series of rash associated with influenza B in school children

Danuta M. Skowronski,a,b Catharine Chambers,a William Osei,c Jill Walker,c Martin Petric,a,b Monika Naus,a,b Yan Li,d,e Mel Krajden,a,b

aBritish Columbia Centre for Disease Control, Vancouver, BC, Canada. bUniversity of British Columbia, Vancouver, BC, Canada. cNorthern Health Authority, Prince George, BC, Canada. dNational Microbiology Laboratory, Winnipeg, MB, Canada. eUniversity of Manitoba, Winnipeg, MB, Canada.

Correspondence: Danuta M. Skowronski, British Columbia Centre for Disease Control, 655 West 12th Avenue, Vancouver, BC, Canada V5Z 4R4.
E-mail: danuta.skowronski@bccdc.ca

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This case series describes morbilliform and other rash presentations among schoolchildren during a March 2014 outbreak of influenza-like illness (ILI) in British Columbia, Canada. Multiplex nucleic acid testing of nasopharyngeal specimens and paired serologic investigations identified that influenza B, characterized as B/Massachusetts/02/2012-like (Yamagata-lineage), was the only viral aetiology and most likely cause of ILI and rash. An association between influenza B and rash has been described infrequently elsewhere, and not previously in North America. Influenza B should be considered in the differential diagnosis of febrile exanthem. Evaluation of the nature, incidence and contributing agent–host–environment interactions, and immunologic mechanisms to possibly explain influenza-associated rash is warranted.

Keywords Exanthem, inactivated, influenza, influenza vaccine, influenza-like illness, morbilliform, rash, vaccine.

Introduction

Late-season influenza B activity occurred in Canada during the 2013–2014 season, with circulating viruses predominantly belonging to the B/Yamagata-lineage included in the 2013–2014 trivalent influenza vaccine (TIV). In March 2014, an outbreak of influenza-like illness (ILI) involving the elementary and high school (~200 students combined) of a rural community (population < 1500) of British Columbia (BC), Canada, was reported, with 15% and 8% of the student populations affected, respectively. Rash associated with ILI was noted in four students, including generalized maculopapular rash in an elementary-school child. Interest in fever associated with rash illness was heightened because of a large measles outbreak occurring simultaneously elsewhere in the province. This case series describes an outbreak of ILI and rash associated with laboratory-confirmed influenza B in schoolchildren.

Methods

Outbreak investigation was conducted under the authority of the Medical Health Officer, and research ethics board approval was not required. Laboratory testing was conducted according to standard protocols at the BC Public Health Microbiology and Reference Laboratory that encourage submission of specimens from up to six patients to arrive at ILI outbreak diagnosis. Further specimens were collected to ensure that ILI cases with rash known to the local health unit were included in diagnostic testing. Nasopharyngeal swabs were tested for influenza by reverse-transcription polymerase chain reaction (RT-PCR) and for respiratory viruses by the Respiratory Virus Panel Luminex assay, which includes targets for influenza A/H3, A/H1 and B; RSV; coronaviruses 229E, OC43, NL63, and HKU1; parainfluenza 1–4; human metapneumovirus A/B; entero/rhinovirus; adenovirus; and bocavirus. Further nucleic acid testing for measles, enterovirus and mumps was conducted. Influenza-positive specimens were sequenced to determine lineage and where possible, virus was isolated in cell culture to determine strain by haemagglutination inhibition (HI) assay. Paired sera were collected, and antibody titres were assessed by HI using live and ether-extracted B/Massachusetts/02/2012-like (Yamagata-lineage) and B/Brisbane/60/2008-like (Victoria-lineage) viruses. Sera were also tested for IgM/IgG to measles, human parvovirus-B19 and rubella. Clinical and epidemiologic information was obtained by local public health staff using a standard questionnaire.
Case series

Six tested students (C1–C6) had laboratory-confirmed influenza B infection, including three (C4–C6) with localized rash (Tables 1 and 2). One additional student (E1) developed generalized rash and was epidemiologically linked through shared classroom exposure to C1 and C5 but was RT-PCR negative for influenza. Illness onset dates ranged March 5–12, ages ranged 6–14 years, and 4/7 were female. ILI symptoms did not substantially differ across cases.

Among the three students with localized rash, two were high-school students in the same grade with erythematous, non-pruritic rash of the back of the hands, sparing the palms, one macular (C4) and one papular (C6; Figure 1A). The third student with localized rash (C5) attended the elementary school and reported facial rash that was erythematous, pruritic, macular and continuous over the cheeks, nose and around the eyes, with conjunctivitis and photophobia.

E1’s rash was erythematous, pruritic and maculopapular, beginning on the arms and face 2 days after ILI onset with spread to the rest of the body, sparing the palms and soles (Figure 1B–D). There was no oral enanthem. Rash persisted 9 days, worsening with exposure to cold air/water. Tearing and photophobia, without conjunctivitis, and nausea, vomiting, abdominal pain and loss of appetite were accompanying symptoms.

None of the students with rash reported change in diet, detergent, or other products in contact with skin, had an allergic history or comorbidity, or took medications in the week before/after symptom onset to explain rash illness. The one exception may be C5 who receives daily aspirin prophylaxis for an unrelated medical condition and completed a 5-day course of amoxicillin for the current ILI episode beginning 2 days prior to rash onset; however, rash did not recur with subsequent use of amoxicillin for another indication. All sought medical care; none were hospitalized. All but one received two measles/mumps/rubella (MMR) vaccine doses, with one single-dose recipient. Only E1 had received the 2013–2014 TTV (inactivated) administered as a single dose 11.5 weeks prior to ILI onset. E1 had also previously received TIV in 2006, 2007 and 2008.

All six influenza-positive specimens were characterized by RT-PCR as B/Yamagata-lineage; of the four viruses that could be isolated in cell culture, all were characterized as B/Massachusetts/02/2012-like (Table 2). Although a nasopharyngeal specimen collected from E1 at 6 days post-ILI onset was influenza negative by RT-PCR, HI antibody titres to B/Massachusetts/02/2012-like virus in sera collected from E1 were comparable to or higher than titres in C1–C6. In all cases, titres were lower in paired sera collected 21–33 days after the first serum. This likely reflects the 8- to 14-day delay from ILI onset to first serum collection, at which point infection-induced titres may have already been peaking and fourfold rise (i.e. sero-conversion) could not subsequently be shown. On balance, serologic findings in E1 are more consistent with recent influenza B infection than prior immunization. In all children, HI titres were higher when using ether-extracted versus live influenza B virus, as expected, but trends were similar. In two children with localized rash (C4, C5), titres were similar or higher to the alternate B/Victoria-lineage compared to the B/Yamagata-lineage strain confirmed by PCR and/or culture to be the cause of their current ILI.

No other viral aetiology was identified based on multiplex nucleic acid testing or serology (Table 2).

Discussion

Here, we describe rash associated with influenza B in schoolchildren during a late-season ILI outbreak. In addition to typical ILI symptoms, three students developed localized rash and one developed generalized morbilliform rash. Six of seven students investigated (including three with localized rash) had laboratory-confirmed influenza B, while the seventh with generalized rash had serologic evidence of infection and was confirmed through epidemiological links to two laboratory-confirmed cases of influenza B in the same classroom (one also with rash). Although amoxicillin may have been a contributing factor in the laboratory-confirmed classmate with localized rash, lack of recurrence with subsequent re-exposure to the same antibiotic argues against allergic aetiology. No co-infection or other viral aetiology was identified in any of the seven ILI cases investigated.

Rash is an uncommon manifestation of influenza. Two prior published reports describe rash with laboratory-confirmed influenza B, both noting morbilliform features: a case report from India in an 11-year-old2 and a case series including six children in Germany aged 4–13 years old with ILI and generalized exanthem and enanthem.5 Hope-Simpson reported ~2% and 8%, respectively, of medically attended influenza A and B infections in a British community between 1962 and 1966 had rash, but rash features were not described.4 Among 151 patients hospitalized with influenza in Australia in 1982, 4 of 56 (7%) <15 years old (and none ≥15 years old) presented with rash; 3/4 were initially diagnosed as measles, and of these three, two were influenza B.5 Among adult Singaporean military recruits, rash (undescribed) was more often associated with influenza A/H3N2 than A (H1N1) pdm09 or influenza B.6 Rash associated with influenza A has been variously characterized as petechial,7,8 macular,7 papular,9 maculopapular,10 reticular9 or purpuric11,12 and has been localized,9 multifocal7,8,12 or generalized,10 pruritic9 and non-pruritic.7 Generalized maculopapular rash associated with
### Table 1. Clinical and epidemiologic features of cases in series

|                  | C1                  | C2                  | C3                  | C4                  | C5                  | C6                  | E1                  |
|------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| **ILI Symptoms** | Fever chills        | Fever               | Fever chills cough  | Fever               | Fever               | Fever               | Fever               |
|                  | Cough               | Cough               | Headache            | Cough               | Cough               | Cough               | Cough               |
|                  | Coryza headache     | Coryza              | Sore throat         | Coryza              | Coryza              | Coryza              | Coryza              |
|                  | Sore throat myalgia  | Headache            | Myalgia arthralgia  | Headache            | Headache            | Headache            | Headache            |
|                  | Prostration         | Prostration         | Prostration         | Prostration         | Prostration         | Prostration         | Prostration         |
| **Other symptoms** | Sneeze              | Sneeze              | Sneeze              | Sneeze              | Sneeze              | Sneeze              | Sneeze              |
|                  | ↓ appetite           | ↓ appetite           | ↓ appetite           | ↓ appetite           | ↓ appetite           | ↓ appetite           | ↓ appetite           |
|                  | Red cheeks           | Conjunctivitis photophobia | Chest pain         | Photosensitivity    | Photosensitivity    | Photosensitivity    | Photosensitivity    |
|                  | Diarrhoea            | Tearing             | Diarrhoea           | Nasea               | Nasea               | Nasea               | Nasea               |
|                  |                     |                     | Diarrhoea           | Vomiting            | Vomiting            | Vomiting            | Vomiting            |
|                  |                     |                     | Diarrhoea           | Abdominal pain      | Abdominal pain      | Abdominal pain      | Abdominal pain      |
| **Duration of ILI symptoms** | 10 days             | 9 days              | 9 days              | 8 days              | 11 days             | 3 days              | 11 days             |
| **Epidemiological links – shared settings among cases in series** |                      |                      |                      |                      |                      |                      |                      |
| School Grade     | Elementary           | Elementary           | Elementary           | High School         | Elementary           | High School         | Elementary           |
| Classroom        | C5, E1              |                     |                     | C6                  |                     |                     | C1, C5              |
| Household        | C2                  | C1                  |                     |                     |                     |                     |                     |
| **Affected body part** | None                | None                | None                | Localized: Back of hands | Localized: Cheeks nose peri-orbital | Localized: Back of hands | Generalized: sparing palms and soles |
| **Type**         | NA                  | NA                  | NA                  | Macular non-itchy   | Macular itchy       | Papular non-itchy   | Maculopapular itchy |
| **Features**     | NA                  | NA                  | NA                  | Followed hot shower | Facial numbness     | None specified      | Worse with cold air/water |
| **Interval from ILI symptom onset to rash onset** | NA                  | NA                  | NA                  | 2 days              | 4 days              | 0 days              | 2 days              |
| **Duration of rash illness** | NA                  | NA                  | NA                  | 1 days              | 4 days              | 3 days              | 9 days              |

ILI, influenza-like illness; NA, not applicable.
influenza A(H1N1) pdm09 spared the palms and soles, as was also noted here for influenza B.10

While no conclusions can be drawn from a single case, it is interesting that the child with generalized rash was the only one in the current series to have received influenza vaccine. Immunization would not have been a direct cause of rash 3 months later but prior sensitization may nevertheless be relevant. Pre-existing vaccine- or infection-induced antibody might be hypothesized to play a role in rash pathogenesis through the rapid formation of antigen–antibody complexes upon re-exposure. In that regard, it is also interesting that 2 of 3 children with localized rash (and no history of prior

| Table 2. Laboratory findings among cases in series |
|--------------------------------------------------|
| **C1** | **C2** | **C3** | **C4** | **C5** | **C6** | **E1** |
| Nasopharyngeal specimen – RT-PCR results |
| Interval from ILI symptom onset to specimen collection |
| 6 days | 0 days | 7 days | 4 days | 5 days | 2 days | 6 days |
| Influenza | B/Yamagata | B/Yamagata | B/Yamagata | B/Yamagata | B/Yamagata | B/Yamagata |
| Enterovirus | Negative | Negative | Negative | Negative | Negative | Negative |
| Measles | Negative | Negative | Negative | Negative | Negative | Negative |
| Mumps | TND | TND | TND | Negative | Negative | Negative |
| Other RV* | Negative | Negative | Negative | Negative | Negative | Negative |
| Characterization of influenza virus isolates – HI assay results |
| Strain | TND** | B/Mass** | B/Mass | B/Mass | TND | B/Mass | NA |
| Nasopharyngeal specimen – RT-PCR results |
| Interval from ILI onset to specimen collection |
| First | 14 days | 8 days | 15 days | 12 days | 14 days | 14 days | 14 days |
| Second | 47 days | 41 days | 40 days | 33 days | 35 days | 35 days | 39 days |
| Influenza serology – inverse HI titre based on ether-extracted virus (geometric mean of duplicate titres)*** |
| B/Massachusetts/02/2012 (Yamagata-lineage)† |
| First | 1810 | 3620 | 226 | 320 | 57 | 160 | 1810 |
| Second | 905 | 905 | 160 | 226 | 57 | 160 | 1280 |
| B/Brisbane/60/2008 (Victoria-lineage)†† |
| First | 14 | 7 | 57 | 320 | 320 | 5 | 5 |
| Second | 5 | 5 | 40 | 160 | 226 | 5 | 7 |
| Influenza serology – inverse HI titre based on live virus (geometric mean of duplicate titres)*** |
| B/Massachusetts/02/2012 (Yamagata-lineage)† |
| First | 113 | 320 | 10 | 20 | 5 | 20 | 160 |
| Second | 80 | 80 | 5 | 20 | 5 | 10 | 80 |
| B/Brisbane/60/2008 (Victoria-lineage)†† |
| First | 5 | 5 | 10 | 113 | 160 | 5 | 5 |
| Second | 5 | 5 | 5 | 40 | 113 | 5 | 5 |
| Other serology |
| Measles IgM/IgG |
| First | NR/R | NR/R | NR/NR | NR/Inconcl | NR/R | NR/R | NR/R |
| Second | NR/R | NR/R | NR/NR | NR/Inconcl | NR/NR | NR/R | NR/R |
| Parvovirus B19 IgM/IgG |
| First | NR/NR | NR/NR | NR/NR | NR/NR | NR/NR | NR/R | NR/NR |
| Second | NR/NR | NR/NR | NR/NR | NR/NR | NR/NR | NR/R | NR/NR |
| Rubella IgG |
| First | R | R | R | R | R | R | R |
| Second | R | R | R | R | R | R | R |

RT-PCR, reverse transcription polymerase chain reaction; TND, test not done; RV, respiratory virus; ILI, influenza-like illness; HI, haemagglutination inhibition; B/Mass, B/Massachusetts/02/2012-like strain; NA, not applicable; NR, non-reactive; R, reactive; Inconcl, inconclusive.

*See text for targets of multiplex respiratory virus panel.

**Sequencing of the haemagglutinin gene from original specimens identified no unusual features and phylogenetic analysis confirmed closest alignment with B/Massachusetts/02/2012-like (clade 2) virus (Genbank numbers: KP083464 and KP083465).

***Titres < 10 assigned a value of 5.

†B/Massachusetts/02/2012-like (Yamagata-lineage) virus is the recommended reference strain for the 2013–2014 TIV.

††B/Brisbane/60/2008-like (Victoria-lineage) virus was the recommended reference strain for the 2009–2010 to 2011–2012 TIV and remains the recommended Victoria-lineage reference virus for 2014–2015 quadrivalent influenza vaccine formulations.
influenza immunization) raised substantial antibody titres to previously circulating B/Victoria-lineage virus, suggesting prior infection-induced priming to epitopes shared with the currently infecting B/Yamagata-lineage strain. Antigen and antibody levels at a precise balance may be required for complex formation and in explaining the unusual occurrence and varying nature of influenza-associated rash, particularly late in the season. Ultimately, proposed mechanisms for influenza-associated rash remain speculative. However, prior receipt of the current season’s TIV is nevertheless important because it may have attenuated the amount and duration of virus shedding, relevant given the negative RT-PCR result in the child with generalized rash and 6-day delay to nasopharyngeal specimen collection. High titres to B/Massachusetts/02/2012-like virus in that child’s sera reinforce the influenza B diagnosis otherwise confirmed through epidemiologic links. Ultimately, however, we cannot rule out other unrecognized aetiologies or contributing factors. Multiplex testing did not identify another viral infection, but the association between influenza and rash does not prove causality; it remains possible that patients in this series were simultaneously infected with an unidentified pathogen or that some other environmental factor contributed.

In conclusion, this is the first report from North America of rash associated with influenza B. Influenza B should be included in the differential diagnosis of febrile exanthem recognizing that, as for influenza A, rash may include varied clinical presentations. Further evaluation of the nature, incidence and contributing agent–host–environment interactions, and immunologic mechanisms to possibly explain influenza-associated rash is warranted.

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Disclosure and competing interest

Within 36 months of manuscript submission, authors have the following potential conflicts of interest to disclose: MK has received unrelated research grants from Roche, Merck, Gen-Probe, Siemens and Boerhinger Ingelheim. The other authors declare that they have no competing interests to report.

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