Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Estimated protective effectiveness of intramuscular immune serum globulin post-exposure prophylaxis during a measles outbreak in British Columbia, Canada, 2014

Mark Bigham *, Michelle Murti, Christina Fung, Felicity Hemming, Susan Loadman, Robert Stam, Paul Van Buynder, Marcus Lem

*Fraser Health Authority, Office of the Chief Medical Health Officer, #400-13450 102 Ave, Surrey, British Columbia V3T 0H1, Canada*

ARTICLE INFO

*Article history:*
Received 23 December 2016
Received in revised form 17 March 2017
Accepted 20 March 2017
Available online xxxx

*Keywords:*
Immune serum globulin
Measles
Post-exposure prophylaxis
Effectiveness

ABSTRACT

*Introduction:* Intramuscular Immune Serum Globulin (IM ISG) is recommended as post-measles exposure prophylaxis (PEP) when administered within 6 days of initial exposure, with variable effectiveness in preventing measles disease. Effectiveness of IM ISG PEP in preventing clinical measles was assessed during a 2014 measles outbreak among a religious-affiliated community in British Columbia, Canada.

*Material and methods:* Fifty-five self-reporting measles susceptible contacts were offered exclusively IM ISG PEP within an eligibility period best surmised to be within 6 days of initial measles case exposure. Clinical outcome of IM ISG PEP recipients was determined by selective active surveillance and case self-reporting. IM ISG PEP failure was defined as onset of a measles-like rash 8–21 days post-IM ISG PEP. Post-IM ISG PEP measles IgG antibody level was tested in 8 recipients. Factors associated with measles disease were analyzed.

*Results:* Seventeen of 55 IM ISG PEP recipients developed clinically consistent measles in the following 8–21 days, corresponding to an estimated crude protective effectiveness of 69%. In school aged children 5–18 years, among whom potential exposure intensity and immune status confounders were considered less likely, estimated IM ISG PEP protective effectiveness was 50%. Age <25 years was significantly associated with breakthrough clinical measles in bivariate analysis ($p = 0.0217$). Among 8 tested contacts of 17 considered IM ISG PEP failures, post-IM ISG PEP measles IgG antibody levels (mean 16.3 days (range 16–17 days) post-PEP) were all <150 mIU/ml.

*Conclusions:* The estimated crude IM ISG PEP protective effectiveness against measles disease within 8–21 days post-ISG administration was 69%. Accuracy of this estimated protective effectiveness is vulnerable to assumptions and uncertainties in ascertaining exposure details and pre-exposure immune status. Increasing the Canadian recommended measles IM ISG PEP dose from 0.25 to 0.5 ml/kg (up to 15 ml maximum volume) may increase protective effectiveness.



## 1. Introduction

Measles is a reportable disease to public health authorities in Canada and the United States. Routine public health follow-up of a reported measles case includes identifying and providing post-exposure prophylaxis (PEP) to susceptible contacts, comprising either measles-containing vaccine (in Canada and the United States, offered as measles-mumps-rubella (MMR) vaccine), or intramuscular administered immune serum globulin (IM ISG) if within 3 or 6 days respectively, of initial exposure to a case.

IM ISG has been offered as PEP to assessed susceptible close contacts of measles cases for over 70 years. The protective effectiveness of IM ISG PEP was initially demonstrated in community trials in the United States during the 1940s. Ordman et al., from a 1942–43 outbreak in Boston, reported an estimated 83% protective effectiveness for IM ISG PEP given to household contacts within 5 days of exposure (compared with a control group of measles household contacts), using dose volumes of 2 ml for infants, 2.5 ml for children 1–5 years and 5 ml for older persons [1]. From a 1943 outbreak in Baltimore and Philadelphia, Stokes et al. reported an estimated 79% protective effectiveness for IM ISG PEP, when given to household contacts within 7 days of exposure (compared with control children from 3 area schools and one institution) at dose volumes of 0.5–5 ml [2].

* Corresponding author.
*E-mail address:* mark.bigham@fraserhealth.ca (M. Bigham).

http://dx.doi.org/10.1016/j.vaccine.2017.03.069
0264-410X/

Unfortunately, these early reports of IM ISG PEP effectiveness did not indicate actual measles antibody dose (e.g. mIU/kg) administered. This is important in the context of declining population measles antibody levels in the United States and other developed countries including Canada, since initial licensure in the United States of measles vaccine in 1963. Since then, universal childhood measles immunization programs have achieved and sustained elimination of endemic measles transmission in the United States and Canada [3–5]. Paralleling this, a trend of decreasing measles antibody titers has been documented in immune globulin products derived from pooled donor plasma [7], related to an increasing proportion of younger plasma donors, who have lower levels of vaccine-induced measles antibody than older plasma donors who had experienced community-acquired measles infection [6,7]. Findings reported by Subbarao et al. were consistent with these trends: 48 h after receiving IM ISG PEP (dose 0.25 ml/kg), only 2 of 15 neonatal intensive care unit infants with baseline seronegative measles results (ELISA value $\leq$0.13, MEASELISA II, Whittaker Bioproducts, Walkersvile MD), were seropositive (ELISA value $\geq$0.16) [8].

Subsequently, King et al. described a small retrospective study of household attack rates from California during measles resurgence in the United States in 1989–90, reporting an estimated IM ISG PEP (dose unspecified) protective effectiveness of only 8% (95% confidence interval: <0–58%) when given within 6 days of initial exposure [9]. Endo et al. reported outcomes after IM ISG PEP administration within 5 days of exposure (mean 3.3 days) to 33 Japanese close contacts (mean age 1.5 years, 32 of 33 $\geq$6 months age). IM ISG PEP dose was 0.33 ml/kg, using ISG lots of variable measles antibody potency between 16–45 IU/ml (i.e. 5.3–14.9 IU/kg). Nine of 33 (27.3%) contacts developed clinical measles. A dose-response effect was observed, with breakthrough measles in 57.1%, 16.7% and 0% of contacts receiving IM ISG PEP doses of 5.3, 10, and >13.2 IU/kg respectively [10].

Sheppeard et al. described IM ISG PEP effectiveness during a 3 month measles outbreak in Australia in 2006 [11]. IM ISG PEP (dose 0.2 ml/kg and potency 32 IU/ml, equivalent to an IM ISG PEP measles antibody dose of 6.4 IU/kg) was offered to susceptible contacts (as per Australian guidelines) within7 days of exposure, with a reported estimated protective effectiveness of 75.8% (95% CI: 0–94). Of note, secondary measles attack rates were not stratified by exposure setting, so differences in exposure intensity between IM ISG PEP recipients and non-recipients may have biased the analysis towards overestimating IM ISP PEP effectiveness.

Overall then, reports from the 1940s during the pre-measles vaccine era of endemic measles transmission and high population measles prevalence, indicated high protective effectiveness of IM ISG PEP against measles. More recent evidence from the post-measles vaccine era, with endemic measles transmission eliminated in many developed countries, has revealed variable clinical benefit of IM ISG PEP. In this paper we describe our recent experience with IM ISG PEP during a measles outbreak in March-June 2014 in British Columbia, Canada, and offer some post-outbreak reflections.

## 2. Material and methods

### 2.1. Description of affected community

In February 2014, measles virus was introduced into a close-knit religious-affiliated rural community of approximately 1200 in the Fraser valley region of southwest British Columbia; this community generally shuns recommended publicly funded childhood or adult immunizations [12]. The likely vehicle of imported measles virus was a returning visitor from the Netherlands, where a large measles outbreak primarily affecting members of a related religious community had been ongoing since May 2013 [13,14]. Public health became aware of an outbreak in early March 2014, as a result of reported school absenteeism due to a febrile, rash illness. A cumulative 433 outbreak-associated cases (325 confirmed and 108 probable, with 419 of 433 (97%) <25 years age) were identified by the regional health authority up to June 2014, almost all involving members of this particular religious community. Most cases and potential contacts were identified through active telephone household syndromic surveillance by public health, focusing on households of Kindergarten-to-grade 12 students attending one school predominantly attended by children from the affected community. A small number of cases and contacts from the community self-reported measles-like illness to public health. Likely, the actual number of cases was higher as many community members choose not to enrol in the provincial health care plan, so are not tracked in administrative data bases, or are reluctant to divulge health information or seek medical diagnosis or treatment [12].

### 2.2. Pre-exposure immune status ascertainment

There was no documented or self-reported prior measles immunization among case contacts within the affected community. Previous measles clusters affecting this community included two reported cases in 1999 as well as small reported clusters in 1986 and 1988; it was therefore inferred that virtually all members of this religious community under 25 years of age were likely susceptible to measles.

### 2.3. Measles exposure ascertainment

Reliable ascertainment of the timing and setting of contacts' initial measles exposure was challenging. Multiple exposures over time and in more than one setting were commonplace. Preschool children were typically household contacts, while school-aged children frequently had both household and school (or also including school bus) exposures. Many adult contacts also reported more than one exposure setting, including school (e.g. school staff), household, church and/or other community events or workplaces.

### 2.4. Post-measles exposure intervention

IM ISG PEP was offered to 57 contacts whose initial exposure was assessed to be within the previous 6 days. In many cases, an exact date of initial measles exposure to an identified case could not be confidently ascertained. One of the 57 contacts was markedly immunosuppressed so in addition to IM ISG PEP, also received 2 supplemental monthly doses of intravenous immune globulin (IVIG); another contact who was pregnant also received IVIG, in addition to IM ISG PEP; these 2 individuals were excluded from further analyses. No susceptible contacts received MMR vaccine PEP.

### 2.5. Assessing post-IM ISG PEP failure

IM ISG PEP recipients were instructed to contact public health if they developed measles-compatible illness. In addition, targeted active contact surveillance was carried out over the subsequent 3 weeks with a large family having a known high risk household contact, and with another individual, to confirm a third-party report of measles. For IM ISG PEP recipients who developed subsequent clinical measles disease, an additional, retrospective assessment could be made of whether IM ISG PEP was offered within the recommended eligibility period. Based on a mean incubation period for measles of 14 days (range 7–21 days) from exposure to onset of rash [15], a minimum interval of 8 days between IM ISG PEP administration and subsequent onset of rash was considered a surrogate indicator that IM ISG PEP was offered within 6 days post-exposure. A potential confounding factor is the possibility

Please cite this article in press as: Bigham M et al. Estimated protective effectiveness of intramuscular immune serum globulin post-exposure prophylaxis during a measles outbreak in British Columbia, Canada, 2014. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.03.069