

# The indications and safety of polyvalent immunoglobulin for post-exposure prophylaxis of hepatitis A, rubella and measles

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## ABSTRACT

Derived from pooled blood donations, polyvalent immunoglobulins are used for post-exposure prophylaxis as one aspect of the public health management of hepatitis A, rubella and measles. This review summarizes the safety profile of these blood products and the current recommendations for their use for the prevention of hepatitis A, rubella and measles among people who have been exposed to these diseases. The current recommendations are drawn from the most recent publicly available national guidelines of the United States, Australia, New Zealand, Canada and the United Kingdom as accessed in February 2019.

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## Introduction

Passive immunization is the transfer of antibodies to a recipient. It occurs during pregnancy, with antibodies being actively transported across the placenta and affording the neonate protection against communicable diseases to which the mother is immune for a number of months post-delivery.<sup>1</sup> Injection or infusion of antibodies from donors is also a form of passive immunization and has been used as a disease prevention tool since the early 20<sup>th</sup> century.<sup>2</sup>

While early forms of passive immunization in the clinical setting involved direct injection of plasma from a person recently recovered from the disease of interest, today's techniques apply the standards of blood product manufacturing.<sup>3,4</sup>

Resulting human immunoglobulin products, both hyperimmune (or 'specific') and normal (or nonspecific) predominantly consist of IgG.<sup>5</sup> Hyperimmune immunoglobulin products include hepatitis B, tetanus, varicella-zoster and rabies immunoglobulins; each containing a known concentration of the particular antibodies.<sup>6</sup> The antibody specificities in normal polyvalent human immunoglobulins (IG) mirror those in the donor population.<sup>7</sup> IG products are available for intramuscular (IMIG) injection and subcutaneous (SCIG) and intravenous infusion (IVIG).<sup>8</sup>

In high-income countries, IG is recommended for the prevention of hepatitis A, rubella and measles in certain circumstances after exposure to someone with the infection, and forms one part of the public health response to these conditions.<sup>6,9–19</sup> The recommendations with respect to this public health intervention are somewhat different in different high-income countries and subject to change with emerging evidence and review of the respective national public health guidelines. There have been a number of such recent guideline reviews.

This review summarizes the safety profile of IG and the current recommendations for use of these products for the

prevention of hepatitis A, rubella and measles among people who have been exposed to these diseases. The current recommendations are drawn from the most recent publicly available national guidelines of the United States, Australia, New Zealand, Canada and the United Kingdom as accessed in February 2019.

## Safety

### *Injection or infusion with IG is generally well tolerated*

The most common side effects of intramuscular injection with IG are local reactions at the injection site. These are almost always minor and resolve spontaneously. They include pain, redness, and stiffness.<sup>12</sup> However, the product is contraindicated for people with severe thrombocytopenia or coagulation disorders because of the potential for hemorrhage into the injected muscle.<sup>20</sup> Other side effects associated with IMIG in the 7 d after injection occasionally include malaise, drowsiness, mild fever, chills, and sweating. Rash, headache, dizziness, nausea, generalized hypersensitivity reactions and convulsions have been reported as rare adverse effects.<sup>20</sup>

The most common side effects that have been related to intravenous IG infusion are said to be reduced by lowering the infusion rate.<sup>21</sup> These include fatigue, nausea, fever, chills, malaise and flushing. Such reactions may occur in 20% or more of people receiving ongoing IVIG therapy.<sup>22</sup> Headache is commonly reported in association with IVIG infusion, and typically responds to mild analgesics or self-resolves. Urticaria is also listed as a common reaction to IVIG infusion and responds to antihistamine or corticosteroid treatment.<sup>21</sup> In contrast, local reactions are rare but include bleeding or bruising at the infusion site.<sup>23</sup> More severe side effects of IVIG infusions are also rare or very rare, with severe side effects occurring in less than 1% of individuals.<sup>22</sup> These include: aseptic meningitis, vasospasm, embolism, vasculitis, encephalopathy, endocolitis, and renal impairment.<sup>21–23</sup>

Subcutaneous infusions seem to result in fewer systemic side effects than intravenous infusions.<sup>23</sup> Local reactions are common to SCIG infusions. These typically include swelling and redness at the infusion site which resolve spontaneously.<sup>23</sup>

With all immunoglobulin products, there is a small chance of anaphylaxis occurring. The risk is said to be increased in people with IgA deficiency.<sup>23</sup> Adrenaline and resuscitation equipment should be on hand when administering IG in a clinical setting.<sup>19</sup> There is also a small chance of infectious disease transmission associated with all immunoglobulin products. Donor screening prior to blood donation, plasma screening and pathogen removal as part of the production process all reduce the risk which, in countries with robust regulatory systems, has been estimated at less than one in a million.<sup>24</sup>

Another potential adverse effect of IG is interference with the immune response to a live virus vaccine.<sup>6</sup> The duration of this adverse effect depends on the dose of immunoglobulin administered. It is thus advisable to wait between 3 and 11 months after the administration of IG before administering measles-mumps-rubella or varicella vaccines.<sup>6</sup> Similarly, it is advisable to wait 3 weeks after giving a live virus vaccine before giving IG if possible.<sup>6</sup>

## Hepatitis A

The recency of published national guidelines for hepatitis A reflects international concerns about declining levels of hepatitis A antibodies in IG products due to increasing population vaccine-induced immunity and decreasing incidence of wild-type virus infections.<sup>25,26</sup> Corresponding contemporary reviews of both the use of vaccination for post-exposure prophylaxis for this disease and the doses of immunoglobulins recommended for passive immunization have occurred.

Vaccination is the mainstay of post-exposure prophylaxis for hepatitis A.<sup>9,16,17,19,27</sup> It is recommended within 2 weeks of exposure for healthy non-immune contacts of hepatitis A from 12 months of age in each of the guidelines examined except for those of Canada, where it is recommended from 6 months of age.

Passive immunization with IMIG is reserved for groups where vaccination is contraindicated or where the risks of severe disease are high. Again, it is typically recommended within 2 weeks of exposure, although for some individuals at highest risk of complications, consideration may be given to passive immunization outside this timeframe.<sup>17</sup> IVIG and SCIG are not currently recommended for the prevention of hepatitis A.

In the United States, IMIG is recommended in addition to the vaccine for adults over the age of 40 years if a risk assessment suggests the person is at increased risk of severe disease; and for people over the age of 12 months who are immunocompromised or have chronic liver disease. IMIG alone is recommended for infants aged less than 12 months. The dose of IMIG recommended regardless of circumstance is 0.1 mL/kg.<sup>16</sup>

In Australia IMIG alone is also recommended for infants <12 months of age, and IMIG in addition to vaccine is recommended for those who are immunocompromised or have chronic liver disease. The Australian guidelines differ from those of the United States in respect of adults over the age of 40 years, recommending risk assessment guide administration of either vaccine, or IMIG, or both. The dose of IMIG also differs, with

contacts lighter than 25 kg recommended 0.5 mL (equivalent to a minimum of 0.02 mL/kg), contacts weighing 25–50 kg recommended 1 mL (equivalent to between 0.04 and 0.02 mL/kg) and contacts weighing more than 50 kg recommended 2 mL (equivalent to a maximum of 0.04 mL/kg). The guideline notes that if longer lasting protection is required, 0.06 mL/kg may be given.<sup>9</sup> Unlike the IMIG products available in the United States, IMIG in Australia is manufactured to the European Pharmacopoeia standard of hepatitis A antibodies.<sup>9,25</sup>

In the United Kingdom, vaccine is preferred over IMIG for those aged 1–59 years. In addition, infants attending childcare are recommended vaccination as post-exposure prophylaxis from 2 months of age. Vaccine and IMIG are advised for adults aged 60 years and over, and also for those with immunosuppression or chronic liver disease.<sup>17</sup> The dose of IMIG is 500 mg (approx. 3.3 mL) for contacts younger than 10 years (equivalent to 0.11 mL/kg for an average nine year old<sup>28</sup>) and 750 mg (5 mL) for contacts aged 10 years or more (equivalent to 0.16 mL/kg for an average 10 year old)<sup>15,28</sup>.

In New Zealand, IMIG alone is recommended for infants aged less than 12 months and may be offered to those contacts who may have a reduced response to vaccination or are at risk of severe disease. The dose recommended is 0.03 mL/kg.<sup>19</sup>

In Canada, IMIG is recommended in addition to vaccine for adults 60 years of age and older, people with chronic liver disease and those who are immunocompromised. IMIG alone is recommended for infants under 6 months of age. In all of these situations, the dose advised is 0.02 mL/kg.<sup>12,27</sup>

## Rubella

In contrast to the guidelines for hepatitis A, those for rubella have not altered since 2013 or earlier.<sup>29,30</sup> Each of the guidelines examined recommends vaccination with a rubella-containing vaccine (MMR) for susceptible individuals exposed to rubella in the absence of contraindications.<sup>6,11,18,19,31,32</sup> The rationale provided is that while unlikely to prevent infection from current exposure, vaccination will prevent infection in the instance of future exposures.<sup>6,11,18,19,32</sup>

Passive immunization is not recommended for non-pregnant contacts in any of the guidelines examined. The Canadian guidelines also do not recommend passive immunization for pregnant contacts.<sup>12,32</sup>

The United States guidelines do not recommend passive immunization for non-immune pregnant contacts unless the pregnant woman will not consider a termination under any circumstances.<sup>11,31</sup> In this case, the recommended dose of IMIG is 20 mL within 72 h of exposure.<sup>31</sup> The guidelines of the United Kingdom and New Zealand similarly advise that passive immunization with IMIG may be considered for non-immune pregnant women where termination is unacceptable or not an option.<sup>18,19</sup> The New Zealand guidelines do not offer a recommended dose. The United Kingdom guidelines advise a dose of 750 mg (5 mL).

Australian guidelines advise that passive immunization of non-immune pregnant women with IMIG may marginally reduce the risk of rubella infection in the fetus and advise a dose of 20 mL within 72 h of exposure with serological follow up for up to 2 months.<sup>6</sup>

## Measles

Each of the guidelines examined recommends measles-containing vaccine (MMR) for healthy non-immune contacts of measles in whom there is no contraindications. There is a general acknowledgment that MMR within 72 h of exposure is efficacious in preventing disease,<sup>10,11,19,33</sup> however, there is also general agreement that MMR beyond this time period may be preferred over IG for healthy individuals given the longer duration of protection afforded by the vaccine.<sup>10,14,19,33,34</sup> Passive immunization is usually reserved for contacts most at risk of severe disease and complications. Each of the guidelines recommends administration of IG within 6 d of exposure, though, particularly for immunocompromised contacts, there is acknowledgment that administration beyond this time period may be considered.<sup>14</sup>

The United States recommends IMIG for infants aged less than 6 months and for infants aged 6–11 months in whom MMR cannot be administered within 72 h of exposure. The dose recommended is 0.5 mL/kg to a maximum of 15 mL. IVIG is recommended for immunocompromised contacts unless they are already receiving adequate doses of IVIG or SCIG as part of the treatment for their condition. IVIG is also recommended for non-immune pregnant women. The dose of IVIG recommended is 400 mg/kg. The guidelines state that IMIG can be used for other non-immune contacts within 6 d of exposure, but that MMR is preferred if administered within 72 h of exposure and that priority for IMIG should be given to contacts with close and prolonged exposure.<sup>11</sup>

Canadian guidelines are similar to those of the United States, recommending IMIG at a dose of 0.5 mL/kg to a maximum of 15 mL for infants aged less than 6 months, and those aged 6–11 months in whom MMR was not administered within 72 h of exposure. However, passive immunization is not generally recommended for healthy non-immune contacts from 12 months of age. In Canada, either IMIG or IVIG is recommended for non-immune pregnant women and immunocompromised individuals (unless receiving adequate doses of IVIG for treatment of their condition) from 6 months of age. Particularly, it is suggested to consider IVIG where the contact weighs more than 30 kg or the volume of IMIG is of concern. The dose of IMIG for these contacts is 0.5 mL/kg to a maximum of 15 mL and the dose of IVIG is 400 mg/kg.<sup>33</sup> The recommendations for IVIG are a recent addition to the Canadian guidelines and coincide with an increase in the volume of IMIG recommended in response to concerns about decreasing concentrations of measles antibodies in the available IG product.<sup>35</sup>

Similar to the Canadian guidelines, the United Kingdom guidelines do not recommend passive immunization for healthy, non-pregnant, non-immune contacts over the age of 8 months.<sup>14,34</sup> IMIG is recommended for infants less than 6 months of age and infants between 6 and 8 months of age who are household contacts of a measles case. The infant dose is 750 mg (5 mL). IMIG is also recommended for non-immune pregnant women. The dose recommended is 2250 mg (15 mL). IVIG is recommended for immunocompromised contacts without evidence of ongoing protection from measles (such as long-term IVIG replacement therapy or serological evidence of immunity) and for those who have had a hematopoietic stem cell transplant within the last 12 months. The dose of IVIG recommended is 0.15 g/kg.<sup>14</sup>

In New Zealand, passive immunization is not recommended for healthy, non-pregnant, non-immune contacts over the age of 15 months. IMIG is recommended for immunocompromised or immune-deficient contacts, non-immune pregnant women, infants less than 6 months of age where there is no evidence of maternal immunity, and infants between 6 and 15 months of age in whom MMR cannot be administered within 72 h of exposure. The dose recommended is 0.6 mL/kg to a maximum of 5 mL for infants and a maximum of 15 mL for those older than 15 months. IVIG is available for measles prophylaxis and can be considered at a dose of 0.15 g/kg for contacts with reduced muscle bulk, where large doses are required, or for contacts with existing ongoing venous access.<sup>19</sup>

Australian guidelines are the only guidelines of those examined where IVIG is not available or recommended for measles post-exposure prophylaxis. IMIG is recommended for infants less than 6 months of age where there is no evidence of maternal immunity, infants between 6 and 8 months of age, infants between 9 and 11 months of age in whom MMR cannot be administered within 72 h of exposure, immunocompromised contacts without recent evidence of immunity, non-immune pregnant women, and other non-immune household contacts where MMR cannot be administered within 72 h of exposure. The guidelines also suggest that IMIG may be considered for use in contacts who are school children or health-care workers. The dose recommended is 0.5 mL/kg for immunocompromised contacts, else 0.2 mL/kg, both to a maximum volume of 15 mL.<sup>10</sup>

## Discussion

Passive immunization as post-exposure prophylaxis is used to varying degrees in high-income countries as a control measure for hepatitis A, rubella and measles. It is an important means of disease prevention for those who are non-immune, have been exposed, and are most at risk of severe disease and complications. Table 1 outlines the products used for hepatitis A, rubella and measles post-exposure prophylaxis in the high-income countries whose guidelines were examined in this review.

IG products are not without their limitations. The disease-specific antibody concentrations in IG products fluctuate between product batches, as well as in the longer term, in accordance with donor antibody levels.<sup>47,48</sup> As the disease-specific antibody dose administered can impact on the effectiveness of disease prevention,<sup>49</sup> specific antibody concentrations in IG products and dosing recommendations need to be periodically reviewed.

Further, the products have a shelf-life and should not be used after the expiry date. As they do not contain preservatives, they should be used immediately upon opening the vials and should not be used if the solution is turbid or contains sediment. Manufacturers' instructions as to storage and administration should be followed.

IG is generally well tolerated by recipients, though anaphylaxis and other severe adverse events are possible in relation to its administration. Particularly for the single dose required for post-exposure prophylaxis, it is advisable that administration is carried out by appropriately trained staff in a clinical setting with

**Table 1.** Polyvalent human immunoglobulin products used in five different high-income countries for post-exposure prophylaxis of hepatitis A, rubella and measles.

| Country                  | Product   | Composition   | Route of administration | Diseases for which product is recommended as post-exposure prophylaxis         |
|--------------------------|---|---|-------------------------|--|
| Australia                | Normal Immunoglobulin-VF <sup>20</sup>  | 160 mg/mL human plasma proteins<br>22.5 mg/mL glycine   | Intramuscular           | Hepatitis A <sup>9</sup><br>Rubella <sup>6</sup><br>Measles <sup>10</sup>      |
| Canada <sup>36,37</sup>  | GamaSTAN S/D <sup>38</sup>  | 150–180 mg/mL human plasma proteins<br>0.21–0.32 M glycine<br>Sodium carbonate  | Intramuscular           | Hepatitis A <sup>27</sup><br>Measles <sup>33</sup>                             |
|                          | IGIVnax <sup>39</sup>   | 100 mg/mL human plasma proteins; glycine  | Intravenous             | Measles <sup>33</sup>  |
|                          | Gammagard Liquid <sup>40</sup>  | 100 mg/mL human plasma proteins; glycine  |                         |  |
|                          | Gammagard S/D <sup>41</sup>   | 50–100 mg/mL human plasma proteins; human albumin; sodium chloride; glycine; glucose; polyethylene glycol; tri(n-butyl)   |                         |  |
|                          | Gamunex <sup>42</sup><br>Privigen <sup>20</sup><br>Panzyga <sup>43</sup>  | 100 mg/mL human plasma proteins; glycine<br>100 mg/mL human plasma proteins; L-proline; hydrochloric acid and/or sodium hydroxide; water for injections<br>100 mg/mL human plasma proteins; glycine; water for injections |                         |  |
| New Zealand              | Normal Immunoglobulin-VF <sup>44</sup>  | 160 mg/mL human plasma proteins<br>22.5 mg/mL glycine<br>Water for injections   | Intramuscular           | Hepatitis A <sup>19</sup><br>Rubella <sup>19</sup><br>Measles <sup>19</sup>    |
|                          | Intragam P <sup>44</sup>  | 60 mg/mL human plasma proteins<br>100 mg/mL maltose<br>Water for injections   | Intravenous             | Measles <sup>19</sup>  |
| United Kingdom           | Subgam <sup>45</sup>  | 160 mg/mL human plasma proteins<br>Sodium chloride<br>Glycine<br>Sodium acetate<br>Polysorbate 80   | Intramuscular           | Hepatitis A <sup>15,17</sup><br>Rubella <sup>18</sup><br>Measles <sup>14</sup> |
|                          | Cuvitru <sup>45</sup>   | 200 mg/mL human plasma proteins; glycine; water for injections  | Intramuscular           | Measles <sup>14</sup>  |
|                          | Gammanorm <sup>45</sup>   | 165 mg/mL human plasma proteins; glycine; sodium chloride; sodium acetate; polysorbate 80; water for injections   |                         |  |
|                          | Hizentra <sup>45</sup>  | 200 mg/mL human plasma proteins; L-proline; polysorbate 80; water for injections  |                         |  |
|                          | Flebogamma DIF <sup>45</sup>  | 50 mg/mL human plasma proteins; D-sorbitol; water for injections  | Intravenous             | Measles <sup>14</sup>  |
|                          | Gammagard S/D <sup>45</sup>   | 50–100 mg/mL human plasma proteins; human albumin; glycine; sodium chloride; glucose monohydrate  |                         |  |
|                          | Gammaplex 10% <sup>45</sup>   | 100 mg/mL human plasma proteins; glycine; polysorbate 80; water for injections; sodium hydroxide; hydrochloric acid   |                         |  |
|                          | Gammaplex 5% <sup>45</sup>  | 100 mg/mL human plasma proteins; glycine; polysorbate 80; water for injections; sodium hydroxide; hydrochloric acid   |                         |  |
|                          | Gamunex 10% <sup>45</sup>   | 50 mg/mL human plasma proteins; D-sorbitol; glycine; sodium chloride; acetate; polysorbate 80   |                         |  |
|                          | Intratect <sup>45</sup>   | 100 mg/mL human plasma proteins; glycine; water for injections  |                         |  |
|                          | IQYMUNE <sup>45</sup>   | 50–100 mg/mL human plasma proteins; glycine; water for injections   |                         |  |
|                          | KIOVIG <sup>45</sup>  | 100 mg/mL human plasma proteins; glycine; water for injections  |                         |  |
| Octagam <sup>45</sup>    | 100 mg/mL human plasma proteins; glycine; water for injections  |   |                         |  |
| Panzyga <sup>45</sup>    | 100 mg/mL human plasma proteins; glycine; polysorbate 80  |   |                         |  |
| Privigen <sup>45</sup>   | 100 mg/mL human plasma proteins; glycine; water for injections  |   |                         |  |
| Vigam <sup>45</sup>      | 50–100 mg/mL human plasma proteins; maltose; water for injections<br>100 mg/mL human plasma proteins; glycine; water for injections<br>100 mg/mL human plasma proteins; L-proline; water for injections<br>50 mg/mL human plasma proteins; human albumin solution 20% added at 2 g/100 ml; sodium n-octanoate; sucrose; sodium acetate; glycine |   |                         |  |
| United States of America | GamaSTAN S/D <sup>46</sup>  | 150–180 mg/mL human plasma proteins<br>0.16–0.26 M glycine  | Intramuscular           | Hepatitis A <sup>16</sup><br>Rubella <sup>11</sup><br>Measles <sup>11</sup>    |
|                          | Bivigam <sup>46</sup>   | 100 mg/mL human plasma proteins; water for injections; glycine; polysorbate 80; sodium chloride   | Intravenous             | Measles <sup>11</sup>  |
|                          | Carimune NF <sup>46</sup>   | 3g, 6g or 12 g human plasma proteins; sucrose; sodium chloride  |                         |  |
|                          | Flebogamma DIF <sup>46</sup>  | 50–100 mg/mL human plasma proteins; D-sorbitol; water for injections; polyethylene glycol   |                         |  |
|                          | Gammagard Liquid <sup>46</sup>  | 50–100 mg/mL human plasma proteins; human albumin; sodium chloride; glycine; glucose; polyethylene glycol; tri(n-butyl)   |                         |  |
|                          | Gammagard S/D <sup>46</sup>   | 50–100 mg/mL human plasma proteins; human albumin; sodium chloride; glycine; glucose; polyethylene glycol; tri(n-butyl)   |                         |  |
|                          | Gammaplex 5% <sup>46</sup>  | 50–100 mg/mL human plasma proteins; human albumin; sodium chloride; glycine; glucose; polyethylene glycol; tri(n-butyl)   |                         |  |
|                          | Gammaplex 10% <sup>46</sup>   | 50–100 mg/mL human plasma proteins; human albumin; sodium chloride; glycine; glucose; polyethylene glycol; tri(n-butyl)   |                         |  |
|                          | Gamunex-C <sup>46</sup>   | phosphate; octoxynol 9; polysorbate 80  |                         |  |
|                          | Octagam <sup>46</sup>   | 50 mg/mL human plasma proteins; D-sorbitol, glycine, polysorbate 80; sodium acetate; sodium chloride  |                         |  |
|                          | Panzyga <sup>46</sup>   | 100 mg/mL human plasma proteins; glycine; polysorbate 80; acetate; sodium chloride  |                         |  |
|                          | Privigen <sup>46</sup>  | 100 mg/mL human plasma proteins; glycine<br>100 mg/mL human plasma proteins; sodium<br>100 mg/mL human plasma proteins; sodium<br>100 mg/mL human plasma proteins; L-proline; sodium                                      |                         |  |

adequate monitoring and accessible resuscitation equipment. Adverse events related to IG should be reported to the relevant therapeutic goods monitoring agency.

Vaccination is the mainstay of hepatitis A post-exposure prophylaxis among those guidelines examined. Passive immunization either in addition to vaccine or alone is recommended for contacts most vulnerable to the disease including those at the extremes of age, and those with pre-existing liver disease or immunocompromise up to 2 weeks post-exposure. IMIG is used for hepatitis A post-exposure prophylaxis in varying doses. The concentration of hepatitis A antibodies in the IMIG available may account for at least some of the dosing variation.<sup>25,26,50</sup>

Neither passive immunization nor vaccination is used to prevent rubella post-exposure in most circumstances. Vaccination is recommended for non-pregnant contacts to provide ongoing protection against future rubella exposures. There are varying recommendations in the guidelines examined in relation to the use of IG to attempt to prevent congenital rubella syndrome. None of the guidelines examined cite a recent Cochrane review on the subject of the effectiveness of passive immunization for preventing rubella.<sup>51</sup> The review concludes that IG seems to be of benefit for preventing rubella up to 5 d after exposure, but notes the lack of evidence directly in relation to the prevention of congenital rubella syndrome.

Given the excellent safety profile of IMIG, meaning the potential benefits are likely to outweigh the risks of its administration, this author suggests passive immunization should be considered as an alternative management option for non-immune pregnant women identified within 5 d of exposure to rubella. A recent modeling study may also offer a means of reviewing the post-exposure dosing recommendations for this purpose.<sup>52</sup>

While vaccination is the mainstay of measles post-exposure prophylaxis and passive immunization is recommended for those most vulnerable to severe disease and complications, the specific definitions of the groups most vulnerable varied considerably in each of the guidelines examined. However, each guideline did identify a subset of infants, pregnant women and those with immunocompromise for whom passive immunization was recommended. Each guideline, with the exception of that from Australia, included recommendations on the use of both IMIG and IVIG for measles prophylaxis, though the recommended doses for each product varied. Some of the variation in dosing may stem from variations in the concentration of measles antibodies in the IG products available. Certainly, the Canadian guidelines have been recently updated as the result of a review of the evidence of effectiveness and the available IG product's measles antibody concentration.<sup>35</sup> Modeling the measured concentration of measles antibodies in the Australian IMIG product has recently led the authors of that study to conclude that IVIG should be added to Australia's measles post-exposure regimen.<sup>52</sup>

While the current guidelines from several high-income countries were examined in this narrative review, it is acknowledged that the review was not inclusive of all countries using IG products for post-exposure prophylaxis. Further, only the publicly available versions of national public health guidelines were included. The review was therefore not able to cover all nuances of public health practice in respect of post-exposure prophylaxis for these diseases around the globe.

This review has summarized the safety and current indications for passive immunization as post-exposure prophylaxis for hepatitis A, rubella and measles in five high-income countries. Contemporary evidence on safety and disease-specific antibody levels in IG products and the effectiveness of passive immunization as post-exposure prophylaxis should continue to inform the revision of national public health guidelines.

## Disclosure of potential conflicts of interest

Megan is a PhD student whose thesis topic is on the effectiveness and efficiency of passive immunization. She is also a public health physician working in the area of communicable disease control. She has no financial conflicts of interest. This manuscript was not grant funded.

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