The Role of Vaccines in Global Disease Prevention

New breakthroughs are giving developing countries the best shot at disease-free living and longevity, but challenges of financing, delivery strategies, efficacy and safety remain.

By Trudie Mitschang
The year is 2020, and the state of the global health landscape is vastly different from the one we see today. Polio and measles have been virtually eradicated worldwide, as have neonatal and maternal tetanus cases. The widespread use of vaccines against pneumococcal, rotavirus, meningococcal and HPV disease have inspired new and more ambitious international health and immunization guidelines, revolutionizing the state of the vaccine marketplace. Perhaps most significantly, breakthrough vaccines have been introduced to combat even the most lethal diseases, including malaria, tuberculosis and HIV/AIDS. Sound like a utopian pipe dream? Perhaps not.

Aggressive growth within the vaccine industry in recent years has resulted in significant achievements, especially when it comes to increasing immunization access in developing countries. Industry analysts predict that by 2020, manufacturers in developing countries may have acquired the capacity to make their own state-of-the-art vaccines tailored to meet their specific needs. Such a contribution to the global vaccine supply could put many of those countries on more equal footing with their industrialized counterparts when it comes to infectious disease control and prevention.

A Surge in Vaccine Development

The first decade of this century has been touted as the most productive in the history of vaccine development. New lifesaving vaccines have been introduced for meningococcal meningitis, rotavirus diarrheal disease, avian influenza caused by the H5N1 virus, pneumococcal disease and cervical cancer caused by human papillomavirus (HPV). According to the World Health Organization (WHO), the next 10 years will spur an increased demand for some of these newer vaccines, especially in developing countries. New vaccine delivery systems are also anticipated, as devices that use needles may largely be replaced with innovative approaches such as aerosol formulations sprayed in the nose (already available in an influenza vaccine) or lungs.¹

Since the year 2000, the vaccine market has almost tripled, exceeding $17 billion in global revenue by mid-2008, and making the vaccine industry one of the fastest growing sectors of industry.¹ Most of this expansion has come from sales in industrialized countries of newer, costlier vaccines, which account for more than half of the total value of vaccine sales worldwide. There are also a large number of candidate vaccines in the late stages of research and development — more than 80, according to recent unpublished data. Furthermore, about 30 of these candidates aim to protect against diseases for which no vaccines are currently available.²

According to a report by WHO, the surge in new vaccine development can be largely attributed to three key factors: the use of innovative manufacturing technology; growing support from public-private product development partnerships; and new funding resources and mechanisms. At the same time, the industry has seen significant growth in the capacity of manufacturers in developing countries to contribute to the supply of traditional childhood vaccines. Since 2000, the demand for these vaccines has grown steadily in an effort to meet the needs sparked by several major initiatives to combat polio, measles and neonatal and maternal tetanus. Currently, there are seven vaccines recommended for distribution and use in developing countries:

- DTP, for diphtheria, tetanus and pertussis
- BCG, for tuberculosis
- measles
- polio
- yellow fever
- hepatitis B
- Haemophilus influenzae type b (Hib)

Expanding immunization coverage for basic vaccines is a proven, cost-effective method for saving lives in the developing world. Globally, increased access to vaccinations has saved more than 20 million children and is widely considered one of the most significant successes in public health. For example, the death rate due to childhood measles has declined 75 percent since the year 2000, while measles immunization rates have increased to 82 percent worldwide since 1990.³ Polio vaccine rates have also seen dramatic increases, thanks in part to the Global Polio Eradication Initiative (GPEI); incidence of the disease went from 350,000 cases in 1988 to 1,652 cases in 2008.⁴

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Envisioning a World Without Polio

In 1988, polio was endemic in 125 countries, resulting in close to 1,000 incidents of paralysis per day.³ That same year, the World Health Assembly (WHA) passed a resolution calling for global eradication of the disease. The GPEI, an international partnership, was initiated to achieve that goal by 2018, and to date, polio eradication efforts have resulted in several landmark successes. For instance, India, long regarded as the nation
Countries at High Epidemic Risk

Meningitis Belt

Facing the greatest challenges to eradication, was removed from the list of polio-endemic countries in February 2012. And, outbreaks in previously polio-free countries were nearly all stopped. Currently, a plan is in place to boost vaccination coverage in Nigeria, Pakistan and Afghanistan, the three remaining polio endemic countries, to levels needed to stop polio transmission. Despite the successes, outbreaks in recent years in China and West Africa due to importations from Pakistan and Nigeria, respectively, highlight the continued threat of resurgence. By some estimates, failure to eradicate polio could lead within a decade to as many as 200,000 paralyzed children a year worldwide. “Polio eradication is at a tipping point between success and failure,” said Dr. Margaret Chan, director-general of WHO. “We are in emergency mode to tip it toward success — working faster and better, focusing on the areas where children are most vulnerable.”

Once achieved, polio eradication would generate net benefits of $40 billion to $50 billion globally by 2035, with the bulk of savings in the poorest countries, calculated based on investments made since the GPEI was formed and savings from reduced treatment costs and gains in productivity. “We know polio can be eradicated, and our success in India proves it,” said Kalyan Banerjee, president of Rotary International, a global humanitarian service organization. “It is now a question of political and societal will. Do we choose to deliver a polio-free world to future generations, or do we choose to allow 55 cases this year to turn into 200,000 children paralyzed for life, every single year?”

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Immunizing the “Meningitis Belt”

Meningococcal meningitis occurs in small clusters throughout the world and accounts for a variable proportion of epidemic bacterial meningitis. The largest burden of meningococcal disease occurs in an area of sub-Saharan Africa comprising 26 countries and known as the “meningitis belt,” which stretches from Senegal in the west to Ethiopia in the east.

In 2001, PATH, an international nonprofit organization, and WHO partnered to create the Meningitis Vaccine Project to develop, test, produce and provide vaccines that prevent meningococcal disease in the meningitis belt. In 2010, the project launched a new vaccine called MenAfriVac using an innovative vaccine-development model involving partners with expertise in technology, materials and manufacturing located on four continents. The vaccine was produced at one-tenth the cost of a typical new vaccine, costing less than 50 cents a dose. It also signified the first time a vaccine was designed specifically for Africa and became the first vaccine ever introduced in Africa prior to reaching any other continent.

According to published materials, MenAfriVac has several advantages over existing polysaccharide vaccines: It induces a higher and more sustainable immune response against group A meningococcus; it reduces the carriage of the bacteria in the throat and, thus, its transmission; it is expected to confer long-term protection not only for those who receive the vaccine, but on family members and others who would otherwise have been exposed to meningitis; it is available at a lower price than other meningococcal vaccines; and it is expected to be particularly effective in protecting children under 2 years of age, who do not respond to conventional polysaccharide vaccines.
Switch to Privigen

Choose the IV Ig therapy that is:

Simple.
- Ready-to-use 10% liquid IV Ig
- 36-month room temperature storage

Sophisticated.
- First and only IV Ig stabilized with proline
- Sucrose-free
- IgA ≤ 25 mcg/mL

Safe.
- 3-step virus inactivation/removal process, including nanofiltration to approximately 20 nanometers, reduces the risk of pathogen transmission. The risk of virus transmission cannot be completely eliminated

Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and history of hypersensitivity.

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have occurred in patients with risk factors; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. Patients could experience increased serum viscosity, hyperproteinaemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IV Ig infusion).

Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to treatment with Privigen. Carefully consider relative risks and benefits before prescribing high-dose regimen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload.

Monitor patients for pulmonary adverse reactions and signs of transfusion-related acute lung injury (TRALI).

Privigen is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies of patients being treated with Privigen for PI, the most serious adverse reaction was hypersensitivity (one subject). Adverse reactions observed in >5% of subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

Privigen is manufactured by CSL Behring AG and distributed by CSL Behring LLC. Privigen is a registered trademark of CSL Behring AG. The Privigen Promise is a trademark of CSL Behring LLC.

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1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA

For more information, call 1-888-310-2525 or visit www.Privigen.com

Guarantee your IV Ig supply for up to 5 years
- Minimize your hospital’s supply risk
- Ensure your patients’ needs are met

Please see brief summary of full prescribing information on following pages.
CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

- Use of Immune Globulin intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, or receiving known nephrotoxic drugs (see Warnings and Precautions [S.2]). Privigen does not contain sucrose.

- For patients at risk of renal dysfunction or failure, administer Privigen at the maximum infusion rate practicable (see Dosage and Administration [2.3], Warnings and Precautions [S.2]).

4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.

- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (see Description [1.1]).

- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (see Warnings and Precautions [S.1]).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (see Contraindications [4]). In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgG (≤25 mg/mL) (see Description [1.1]). Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgG. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur with the use of IGIV products, including Privigen. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. If renal function deterioration continues, consider discontinuing Privigen. For patients judged to be at increased risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable (see Boxed Warning, Dosage and Administration [2.3]).

5.3 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen. Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols or monoclonal gammapathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable (see Boxed Warning, Dosage and Administration [2.3]).

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hypoatremia

Hyproptenemia, increased serum viscosity, and hypoatremia may occur following treatment with IGIV products, including Privigen. The hypoatremia is likely to be a pseudohypoatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolal gap. It is critical to distinguish true hypoatremia from pseudohypoatremia, as treatment aimed at decreasing serum free water in patients with pseudohypoatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently following treatment with Privigen (see Adverse Reactions [6]) and other human globulin products. Discontinuation of treatment has resulted in remission of AMS within several days without sequelae. AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

Privigen may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a potential direct antiglobulin reagent test (DART) (Coombs’ test) result and hemolysis. Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported. Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of Privigen. The likelihood can be associated with the dose of hemolysins: high doses (e.g., ≥2 g/kg), whether given either as a single administration or divided over several days; non-0 blood group; and underlying inflammatory state. Hemolysis has been reported following administration of IGIV for indications including ITP and PL.

Monitor patients for clinical signs and symptoms of hemolysis. If these are present after a Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate stabilizers for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in Privigen preparations. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

5.9 Transmissible Infectious Agents

Because Privigen is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Privigen. Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6955.

5.10 Interference with Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS

The most serious adverse reactions observed in clinical study subjects receiving Privigen for PI were hypersensitivity in one subject. The most common adverse reactions observed in <5% of clinical study subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in <5% of clinical study subjects with chronic ITP were headache, pyrexia/pyrexia, positive DAT, anemia, vomiting, nausea, hyperthermia, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased.

6.1 Clinical Trials Experience

Because different clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Treatment of Primary Humoral ImmuneDeficiency

In a prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CID) received Privigen every 3 or 4 weeks for up to 12 months (see Clinical Studies [14.1]). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69, 46 (57.5%) were male and 34 (42.5%) were female. The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions in Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule.

Routine predmedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by predmedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received predmedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during an infusion or within 72 hours after the end of an infusion, irrespective of causality. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.
Table 2: PI Pivotal Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of an Infusion, Irrespective of Causality

<table>
<thead>
<tr>
<th>Adverse Reaction (Excluding infections)</th>
<th>Number (% of Subjects [n=80])</th>
<th>Number (Rate) of Infusions with Adverse Reaction [n=1038]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>35 (43.8)</td>
<td>82 (0.079)</td>
</tr>
<tr>
<td>Pain</td>
<td>20 (25.0)</td>
<td>44 (0.042)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (16.3)</td>
<td>27 (0.026)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (12.5)</td>
<td>19 (0.018)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>9 (11.3)</td>
<td>15 (0.014)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (8.8)</td>
<td>13 (0.013)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (7.5)</td>
<td>10 (0.010)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (6.3)</td>
<td>5 (0.005)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (6.3)</td>
<td>5 (0.005)</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>5 (6.3)</td>
<td>5 (0.005)</td>
</tr>
</tbody>
</table>

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be at least possibly related to the infusion of Privigen (including 5 serious, severe AEs described below). Of these, 91 were mild, 81 were moderate, 19 were severe, and 1 was of unknown severity.

Table 3: PI Pivotal Study – Adverse Reactions Occurring in >5% of Subjects, Irrespective of Time of Occurrence

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number (% of Subjects [n=80])</th>
<th>Number (Rate) of Infusions with Adverse Reaction [n=1038]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24 (30.0)</td>
<td>62 (0.060)</td>
</tr>
<tr>
<td>Pain, all types*</td>
<td>12 (15.0)</td>
<td>26 (0.025)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (12.5)</td>
<td>18 (0.017)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (11.3)</td>
<td>16 (0.015)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>9 (11.3)</td>
<td>15 (0.014)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (7.5)</td>
<td>11 (0.011)</td>
</tr>
</tbody>
</table>

* Includes abdominal pain lower, abdominal tenderness, arthralgia, back pain, chest pain, infusion-site pain, injection-site pain, neck pain, pain in extremity, and pharyngolaryngeal pain.

† Some subjects experienced more than one type of pain.

Sixteen (20%) subjects experienced 41 serious AEs. Five of these AEs (hypersensitivity, chills, fatigue, diziness, and increased body temperature; all severe) were related to Privigen, occurred in one subject, and resulted in the subject’s withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative DAT at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV virus (B19V).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privigen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subsets were treated with Privigen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.8%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min (see Dosing and Administration [2.3]). The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

In this study, the proportion of infusions temporarily associated with one or more AEs occurring during a Privigen infusion or within 72 hours after the end of an infusion was 15%. The total number of temporally associated AEs, irrespective of causality, was 206 (a rate of 0.27 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Of the 206 temporally associated AEs reported for the 55 subjects with PI, the investigators judged 125 to be at least possibly related to the infusion of Privigen. Of these, 76 were mild, 40 were moderate, and 9 were severe.

Eleven (20%) subjects experienced 17 serious AEs, none of which were considered to be related to Privigen. Three subjects experienced AEs that were considered to be at least possibly related to Privigen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild uticaria in one subject, resulting in the subject’s withdrawal from the study.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 6: Chronic ITP Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of a Treatment Cycle, Irrespective of Causality (Two consecutive daily infusions)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number (% of Subjects [n=114])</th>
<th>Number (Rate) of Infusions with Adverse Reaction [n=114]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>41 (36.9)</td>
<td>41 (0.360)</td>
</tr>
<tr>
<td>Pyrexia/hyperthermia</td>
<td>21 (18.3)</td>
<td>22 (0.193)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (5.3)</td>
<td>6 (0.052)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6 (5.3)</td>
<td>6 (0.053)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (5.3)</td>
<td>6 (0.053)</td>
</tr>
<tr>
<td>Blood unconjugated bilirubin increased</td>
<td>6 (5.3)</td>
<td>6 (0.053)</td>
</tr>
<tr>
<td>Blood conjugated bilirubin increased</td>
<td>5 (8.8)</td>
<td>5 (0.044)</td>
</tr>
<tr>
<td>Blood total bilirubin increased</td>
<td>5 (3.3)</td>
<td>3 (0.026)</td>
</tr>
<tr>
<td>Hemocrit decreased</td>
<td>3 (5.3)</td>
<td>3 (0.026)</td>
</tr>
</tbody>
</table>

Of the 149 non-serious AEs related to Privigen, 103 were mild, 37 were moderate, and 9 were severe.

Three subjects experienced three serious AEs, one of which (aspecific meningitis) was related to the infusion of Privigen.

One subject withdrew from the study due to gingival bleeding that was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention; these cases resolved uneventfully.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure. The following adverse reactions have been identified and reported during the post-approval use of IGIV products: 13

- **Infusion Reactions:** Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rige s, back pain, myalgia, arthralgia, and changes in blood pressure.
- **Renal:** Acute renal dysfunction/failure, osmotic nephropathy.
- **Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm.
- **Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension.
- **Neurological:** Coma, loss of consciousness, seizures, tremor, aseptic meningitis, stroke.
- **Gastrointestinal:** Hepatic dysfunction, abdominal pain.
- **General/Body as a Whole:** Pyrexia, rigors.
It is hoped that all 26 countries in the African meningitis belt will have introduced this vaccine by 2016. High coverage of the target age group of 1 year to 29 years has the potential to eliminate meningococcal A epidemics from this region of Africa.7

Fighting Measles and Rubella in Rwanda

Launched in March of this year, Rwanda’s measles-rubella (MR) vaccination campaign is the beginning of an effort to vaccinate more than 700 million children under 15 years of age against these two disabling and deadly diseases. The combined MR vaccine will be introduced in 49 countries by 2020 thanks to financial support from the GAVI Alliance, a public-private partnership committed to saving children’s lives and protecting people’s health by increasing access to immunization in developing countries. The support builds on the efforts of the Measles & Rubella Initiative (M&RI) that have helped countries to protect 1.1 billion children against measles since 2001. The initiative is a partnership of many health agencies, vaccine companies, donors and others, but it is led by the American Red Cross, the United Nations Foundation, the Centers for Disease Control and Prevention, UNICEF and WHO.

Because of this initiative, Rwanda became the first sub-Saharan African country to provide MR vaccine nationwide with GAVI support. The vaccine will stop not only the transmission of rubella from mother to child, preventing children being born with severe birth defects, but also protect children against measles, which is highly contagious. Every year, an estimated 112,000 children, mostly in Africa, South Asia and the Pacific Islands, are born with handicaps caused by their mothers’ rubella infections. “Rwanda has made great strides over the past four years in child survival by introducing vaccines against leading child killers, including pneumonia and diarrhea,” said Dr. Agnes Binagwaho, Rwanda’s Minister of Health. “The introduction of the combined measles-rubella vaccine is one more important step to ensuring that all children in Rwanda receive the full immunization package. In our efforts to eliminate measles, we have raised measles coverage through campaigns and routine immunization to higher than 95 percent.”8

Five other countries — Bangladesh, Cambodia, Ghana, Senegal and Vietnam — are expected to introduce the MR vaccine through vaccination campaigns with GAVI support by the end of 2013. “Investing in rubella will provide a much-needed boost to improving women’s and children’s health in poor countries. GAVI’s support for measles-rubella campaigns will help accelerate global progress in controlling two life-threatening diseases,” said Dr. Seth Berkley, GAVI Alliance CEO. “Rubella vaccine has been available since the 1970s in many parts of the world. Accelerating the introduction of rubella vaccine in developing countries will spread the benefits of the vaccine to those in most need and build on country efforts to control measles with a cost-effective combined vaccine. It brings us one step closer to ensuring that every child everywhere is fully immunized.”8

Promising Malaria Vaccine Faces Setbacks

There is currently no vaccine that offers complete protection against malaria, but hopes have been high regarding RTS,S, the
most advanced candidate malaria vaccine developed by GlaxoSmithKline (GSK). Unfortunately, in March 2013, a study published in the *New England Journal of Medicine* showed the effectiveness of the vaccine wanes over time, with the shot protecting only 16.8 percent of children over 4 years, according to trial data. The disappointing results raised further questions about whether RTS,S can make a difference in the fight against the disease, a major cause of illness and death among children in sub-Saharan Africa. Results from a separate trial last year showed the vaccine was only 30 percent effective in babies. The new data found that although RTS,S initially had a protection rate as high as 53 percent, after an average of eight months, that effectiveness faded swiftly. “It was a bit surprising to see the efficacy waned so significantly over time. In the fourth year, the vaccine did not show any protection,” said Ally Olotu of the Kenya Medical Research Institute (KEMRI) Wellcome Trust Research Programme in Kenya, who led the follow-up study.

Malaria, caused by a parasite carried in the saliva of mosquitoes, is endemic in more than 100 countries worldwide. According to WHO, malaria infected around 219 million people in 2010, killing some 660,000 of them. Control measures such as insecticide-treated bed nets, indoor spraying and anti-malaria drugs have helped cut malaria cases and deaths significantly in recent years, but drug resistance is growing, and experts say an effective vaccine could be a vital tool in eradicating the disease.

Phillip Bejon, another researcher at KEMRI, asserts there is still a clear benefit to the GSK vaccine. “Many of the children (in Africa) will experience multiple episodes of clinical malaria infection, but overall we found that 65 cases of malaria were averted over the four-year period for every 100 children vaccinated,” he said. “We now need to look at whether offering a vaccine booster can sustain efficacy for longer.”

**Addressing the Cold Chain Challenge**

HIV, malaria and tuberculosis have long represented major global health challenges. Although promising research is underway to develop vaccines for these diseases, considerable hurdles remain for countries where transporting and storing live vaccines in a continuously cold environment (around 2 degrees Celsius to 8 degrees Celsius or below) is simply not possible. If a cold chain cannot be maintained for a live vaccine, there is a high risk it could become unsafe and lose effectiveness.

A recent published study by scientists at King’s College London may offer promise in overcoming this hurdle. Results of the study demonstrated the ability to deliver a dried live vaccine to the skin without a traditional needle, and showed for the first time that this technique is powerful enough to enable specialized immune cells in the skin to kick-start the immunizing properties of the vaccine. “We have shown that it is possible to maintain the effectiveness of a live vaccine by drying it in sugar and applying it to the skin using microneedles — a potentially painless alternative to hypodermic needles,” said Dr. Linda Klavinskas from the Peter Gorer Department of Immunobiology at King’s College London. “We have also uncovered the role of specific cells in the skin which act as a surveillance system, picking up the vaccine by this delivery system and kick-starting the body’s immune processes.”

The report went on to state that the discovery opens up the possibility of delivering live vaccines in a global context, without the need for refrigeration. It could potentially reduce the cost of manufacturing and transportation, improve safety and avoid the need for hypodermic needle injection, reducing costs and increasing accessibility.**Meningitis Key Facts**

- Meningococcal meningitis is a bacterial form of meningitis, a serious infection of the thin lining that surrounds the brain and spinal cord.
- The meningitis belt of sub-Saharan Africa, stretching from Senegal in the west to Ethiopia in the east, has the highest rates of the disease.
- Group A meningococcus accounts for an estimated 80 percent to 85 percent of all cases in the meningitis belt, with epidemics occurring at intervals of seven to 14 years.
- In the 2009 epidemic season, 14 African countries implementing enhanced surveillance reported 88,199 suspected cases, including 5,352 deaths, the largest number since a 1996 epidemic.
- Several vaccines are available to control the disease: a meningococcal A conjugate vaccine, C conjugate vaccines, tetravalent A, C, Y and W-135 conjugate vaccines and meningococcal polysaccharide vaccines.

the risk of transmitting bloodborne disease from contaminated needles and syringes. “This new technique represents a huge leap forward in overcoming the challenges of delivering a vaccination program for diseases such as HIV and malaria. But these findings may also have wider implications for other infectious disease vaccination programs, for example infant vaccinations, or even other inflammatory and autoimmune conditions such as diabetes,” said Klavinskis.

A Commitment to the Future

In recent years, efforts to develop and deliver vaccines to the world’s poorest countries have been on the upswing. In January 2010 at the World Economic Forum, the Bill & Melinda Gates Foundation launched the Decade of Vaccines by pledging $10 billion over 10 years to support worldwide vaccination efforts. The foundation also challenged other global partners to demonstrate their continuing commitment, with a singular goal in mind: to dramatically reduce child mortality by the end of the decade. The effort is an ambitious one, and stakeholders agree there is no easy formula for success. Achieving this goal will require a multipronged approach, including the strengthening of current health systems and immunization programs; new public-private partnerships for vaccine development; new long-term global financing mechanisms; innovative and sustainable delivery strategies; and improved advocacy and communication.

The good news is that today, as never before, governments have an unprecedented number of partners willing to help pay for vaccines and immunization. In a media release following the announcement of the Decade of Vaccines pledge, Dr. Christopher Elias, president and CEO of PATH, said: “The commitment announced by Bill and Melinda Gates will have a tremendous impact on children and families in the poorest areas of the world. PATH is committed, as is the Bill & Melinda Gates Foundation, to letting no child die from a preventable disease, and we are heartened by their continued efforts to move us one step closer toward a world where health is within reach for everyone.”

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References