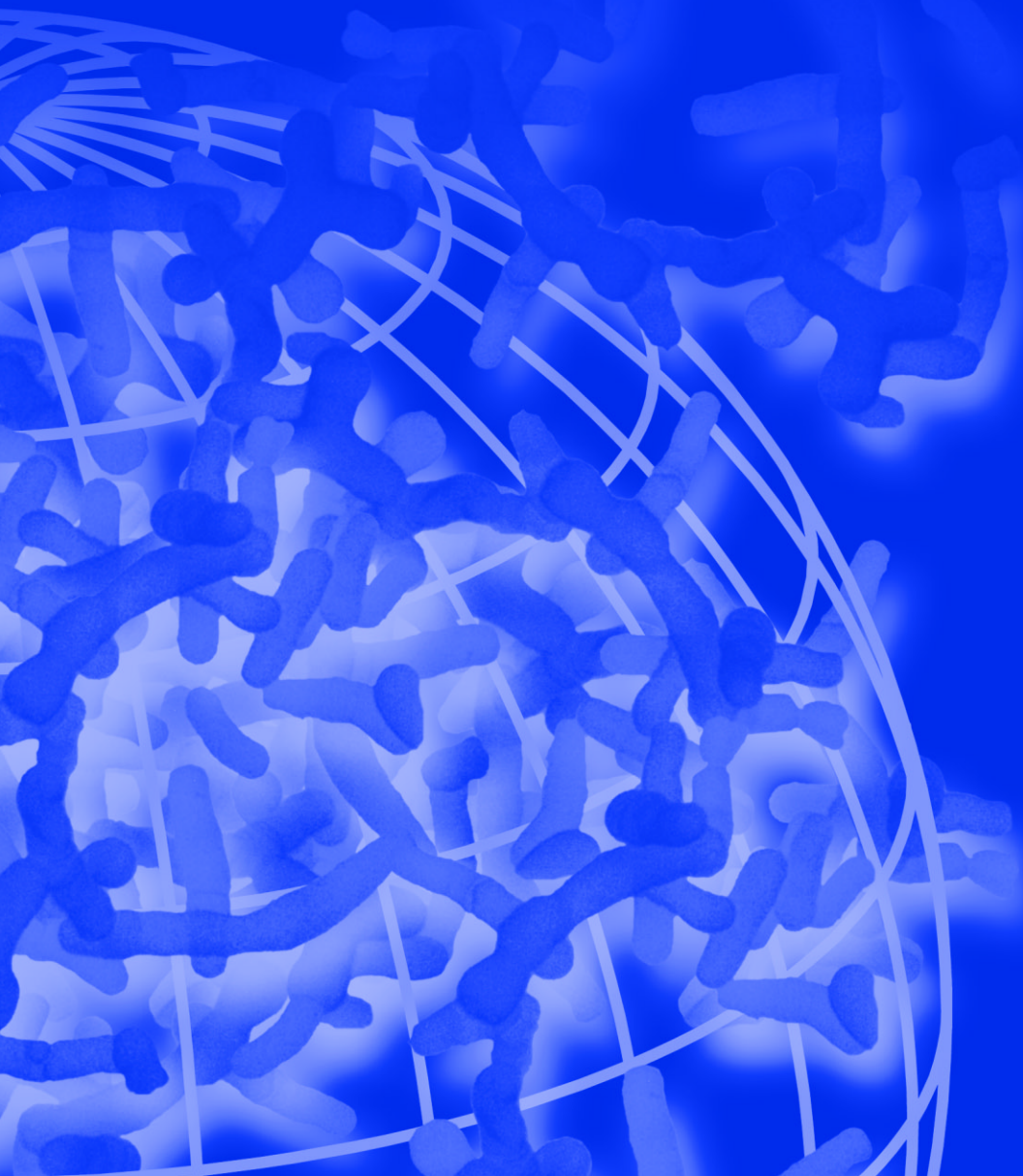
Emerging Pathogens: Real Solutions



Section 1: Emerging pathogens are an ongoing risk

Throughout history emerging pathogens have had a devastating impact on human populations. Despite dramatic advances in understanding the pathophysiology of disease and medical technology, emerging pathogens continue to cause outbreaks, which, with the ease of worldwide travel and commerce, can rapidly spread globally.

Some of these pathogens have been around for decades, and their re-emergence as newer, sometimes more deadly forms can threaten the blood supply. Healthcare authorities worldwide are concerned. Examples of emerging and re-emerging pathogens include simian foamy virus, Ebola virus, human immunodeficiency virus (HIV), orthopoxvirus, enterovirus 71, West Nile virus, Nipah virus, hantavirus, coronavirus, and the variant Creutzfeldt-Jakob disease (vCJD)-causing agent (prion).

Though current scientific knowledge and technical capabilities permit rapid identification of some agents, not all agents are quickly identified. As a result, blood-borne pathogens have evaded detection and continue to emerge at a rapid and unpredictable rate.

Supporting references

- Smolinski MS, Hamburg MA, Lederberg J, eds. *Microbial Threats to Health: Emergence, Detection, and Response.* Washington, DC: The National Academies Press; 2003:1-17.
- Hajjeh RA, Relman D, Cieslak PR, et al. Surveillance for unexplained deaths and critical illnesses due to possibly infectious causes, United States, 1995-1998. *Emerg Infect Dis.* 2002;8:145-153.
- U.S. Department of Health & Human Services. Centers for Disease Control and Prevention. *Preventing Emerging Infectious Diseases: A Strategy for the 21st Century.* Atlanta, Ga: October 1998.

Section 2: Many factors contribute to the emergence of new pathogens

New pathogens appear to be emerging at an increasing rate, which may be attributed to many different factors, a few of which are highlighted here.

- *Encroachment on habitat*
  In search of land and other resources, human beings are encroaching on previously uninhabited and isolated areas such as tropical rainforests. As a result many more animal species are living closer to human populations and domesticated animals than ever before. Thus pathogens are much more likely to cross over from wild animals to humans and livestock, with increased likelihood for human-to-human transmission.

- *Viral adaptation and mutation*
  Infectious diseases have been shown to adapt or mutate because of selection pressures. As a result, zoonotic viruses that usually infect animals may now infect humans to varying degrees. Also as a result of virus mutability, previously benign viruses can become more virulent and more infectious, increasing the likelihood of an epidemic or pandemic. These mutations also make the detection and identification of emerging viruses a challenge for public health officials.

- *Human population explosion and crowding*
  The increase in human population has led to densely populated urban areas that allow infectious diseases to spread very quickly. This change in population density combined with the ease of worldwide travel and the increase in global commerce has removed geographic barriers and encouraged the rapid spread of infectious diseases.

- *Limited governmental resources*
  Public health efforts have helped to slow or even stop the spread of infectious diseases, but many of the countries most affected are developing countries, which have the smallest number of resources to devote to quelling outbreaks.

- *Disease characteristics*
  The characteristics of an infectious disease can also contribute to its ease of spread. A pathogen with a long incubation period and mild clinical profile can spread disease quickly and widely before it is identified and contained by public health authorities. Some of these pathogens, including the vCJD-causing agent (prion), hepatitis C, and HIV, can be deadly.

Supporting references

- Jacobson A. “Emerging and re-emerging viruses: an essay.” Department of Microbiology, University of Capetown, 1994. http://www.mcb.uct.ac.za/ebola/ebolaess.html. Accessed February 9, 2004.
- Dodd RY. Emerging infections, transfusion safety, and epidemiology. *N Engl J Med.* 2003;349:1205-1206.
- Chamberland M, Alter H, Busch M, Nemo G, Ricketts M. Emerging infectious disease issues in blood safety. *Emerg Infect Dis*. 2001;7(3, suppl):552-553.
- Nathanson N. Emergence of new viral infections: implications for the blood supply. *Biologicals.* 1998;26:77-84.

Section 3: Hemophilia patients are particularly susceptible to emerging pathogens

Although anyone who receives blood products is at risk of infection from blood-borne pathogens, persons with hemophilia are particularly susceptible because they frequently use clotting factors, some of which contain or are derived from human plasma, to prevent or control bleeding episodes.

Bulk fractionation is commonly employed to produce plasma-derived Factor VIII (pdFVIII) concentrate, and often plasma donations from many donors are pooled to make a single lot. If a new, unknown pathogen cannot be detected during blood donation, and therefore not removed from the donor pool, or if it is not reduced or removed as a consequence of the bulk fractionation steps, it can infect the recipients of clotting factors derived from plasma. Recombinant Factor VIII (rFVIII) was developed to reduce the dependence on plasma. Until recently, all rFVIII therapies were made with the addition of human and/or animal plasma proteins (eg, albumin) during processing.

Supporting references

- Wilde JT. HIV and HCV coinfection in haemophilia. *Haemophilia*. 2004;10:1-8.
- Centers for Disease Control and Prevention. Blood safety monitoring among persons with bleeding disorders–United States, May 1998-June 2002. *MMWR Morb Mortal Wkly Rep.* 2003;51:1152-1154.
- Evatt BL, Farrugia A, Shapiro, AD, et al. Haemophilia 2002: Emerging risks of treatment. *Haemophilia.* 2002;8:221-229.
- Nolan RC, Chidlow G, French MA. Parvovirus B19 encephalitis presenting as immune restoration disease after highly active antiretroviral therapy for human immunodeficiency virus infection. *Clin Infect Dis.* 2003;36:1191-1194.

Section 4: Technology used in processing plasma-derived therapeutics reduces pathogen risk, but does not eliminate it

Technology used today to reduce or inactivate pathogens in the plasma supply is highly effective, but not necessarily so against emerging pathogens—especially those that have not yet been detected or identified.

Over the years, new technologies have been developed that have dramatically improved the pathogen safety profile of plasma-derived and recombinant clotting factor concentrates. The risk of contamination of products derived from blood has been minimized by improved plasma screening technologies, which often include identification of transmissible pathogens by PCR and serological methods, and by removal or inactivation of infectious agents by fractionation and the use of dedicated viral inactivation technologies. Furthermore, recent generations of rFVIII concentrates are also subjected to viral inactivation techniques that are highly efficient against lipid enveloped viruses (eg, West Nile virus).

Viruses without lipid envelopes (eg, parvovirus B19, hepatitis A virus), however, are far less susceptible to current viral inactivation technologies. Although current data indicate minimal risk to the hemophilia population, recent reports of vCJD transmission through blood transfusion have heightened concern. Further work is needed to improve screening capabilities and to validate the efficacy of prion and nonlipid-enveloped virus removal technologies to better ensure the safety of the blood supply.

Supporting references

- Stramer SL, Glynn SA, Kleinman SH, et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. *N Engl J Med.* 2004;351:760-768.
- Goodnough LT. Risks of blood transfusion. *Crit Care Med.* 2003;31(suppl):S678-S686.
- Kreil TR, Berting A, Kistner O, Kindermann J. West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. *Transfusion.* 2003;43:1023-1028.
- Llewelyn CA, Hewitt PE, Knight RS, et al. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet.* 2004;363:417-421.

Section 5: Setting the goal to achieve "absolute zero risk" for infectious agents

Since the effectiveness of inactivation techniques against future emerging blood-borne pathogens cannot be guaranteed, the only sure way to eliminate the risk of infection associated with the use of plasma protein additives is to remove all human and animal-derived plasma protein additives from rFVIII processing.

A recommendation by the US National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) states that, "all efforts should be made to remove human albumin from recombinant factor VIII products," and that "increased efforts should be made to eliminate human and bovine proteins from the manufacturing process of recombinant products." Similar recommendations have also been made by the United Kingdom Haemophilia Centre Doctors' Organisation.

Supporting references

- Evatt BL, Farrugia A, Shapiro, AD, et al. Haemophilia 2002: Emerging risks of treatment. *Haemophilia.* 2002;8:221-229.
- National Hemophilia Foundation. MASAC recommendations concerning the treatment of hemophilia and other bleeding disorders. MASAC Document #151, November 2003.
- United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO). Guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia.* 2003;9:1-23.

Section 6: The first and only plasma/albumin-free method recombinant Factor VIII therapy

Only ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] eliminates the risk of pathogen transmission from plasma protein additives. That is because ADVATE is the only recombinant FVIII therapy processed without adding plasma or albumin.

Supporting references

- Ewenstein BM, Collins P, Tarantino MD, et al. Hemophilia therapy innovation: development of an advanced category recombinant factor VIII by a plasma/albumin-free method. Proceedings of a Special Symposium at the XIXth Congress of the International Society on Thrombosis and Haemostasis, July 12-18, 2003, Birmingham, UK. *Semin Hematol.* 2004;41(suppl 2):1-18.
- Négrier C, Astermark J, Pabinger I, et al. Surgical evaluation of ADVATE rAHF-PFM, an advanced category recombinant antihemophilic factor prepared using a plasma/albumin-free method. *Blood.* 2003;102:795a. Abstract 2944.
- Tarantino MD, Collins PW, Hay CRM, et al. Clinical evaluation of an advanced category antihaemophilic factor prepared using a plasma/albumin-free method: pharmacokinetics, efficacy, and safety in previously treated patients with haemophilia A. *Haemophilia.* 2004;10:1-10.
- National Hemophilia Foundation. MASAC recommendations concerning the treatment of hemophilia and other bleeding disorders. MASAC Document #151, November 2003.
- ADVATE Prescribing Information. Westlake Village, Calif: Baxter Healthcare Corporation; 2003.

Important safety information:

ADVATE rAHF-PFM should be administered cautiously in patients with previous hypersensitivity to constituents of Factor VIII preparations or known sensitivity to mouse or hamster proteins.

The most common related adverse reactions observed during the ADVATE rAHF-PFM clinical studies include: strange taste in mouth, headache, dizziness, and redness of the face.

The formation of inhibitors has been observed with all Factor VIII products, including ADVATE.

Indication:

ADVATE is indicated for the prevention and control of bleeding episodes in patients with hemophilia A. In Australia and Europe, this includes prophylactic use. In Australia and the United States, this includes perioperative use.

Product Information is available at the Baxter exhibit booth.

Supporting references

- European Summary of Product Characteristics.
- US Prescribing Information.
- Australian Product Information.

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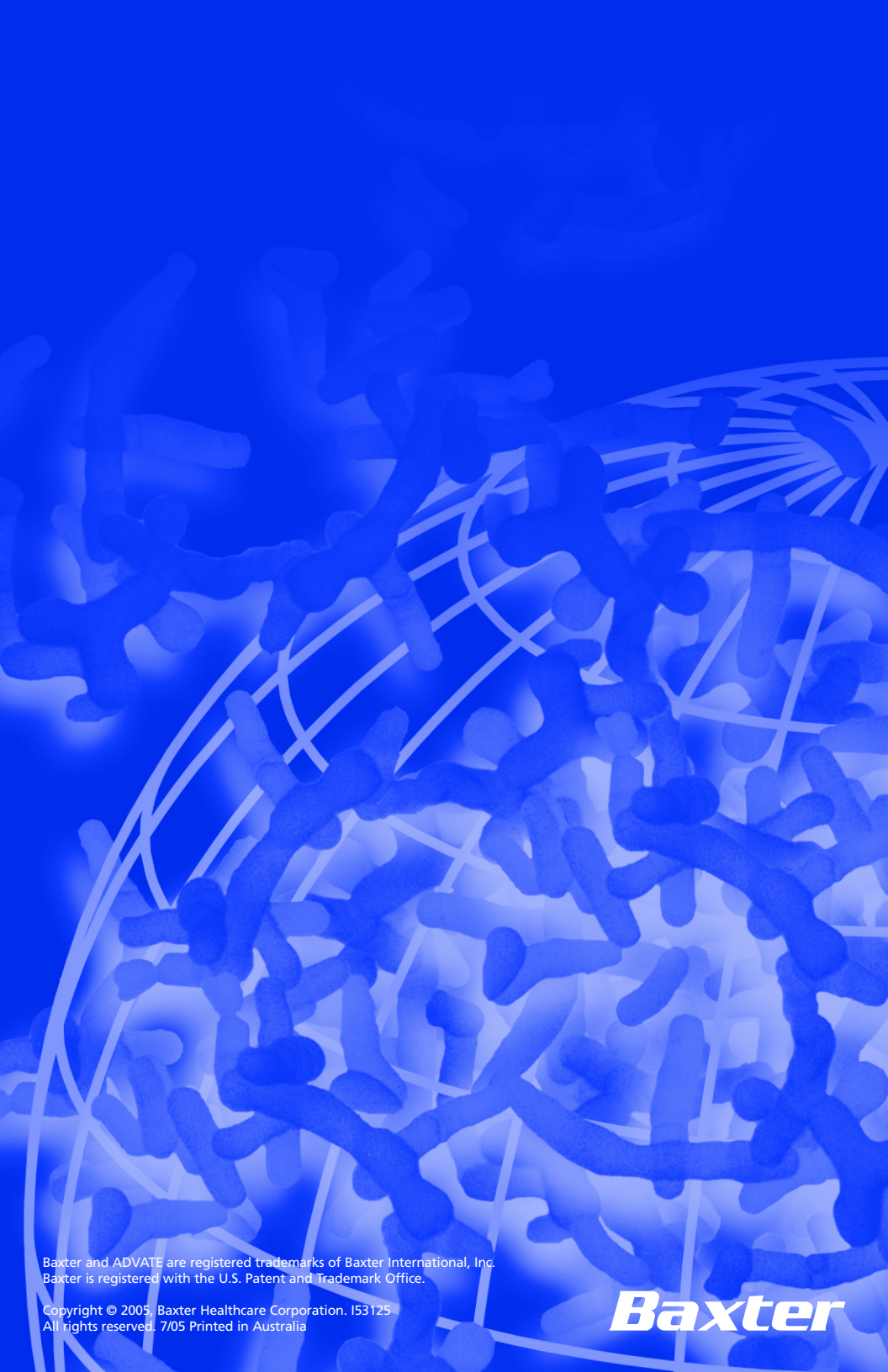

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