

Bildercollage © Gorodenkoff/shutterstock.com; U.PSD/shutterstock.com; PublicDomainPictures/pixabay.com

Parvovirus B19 Implications for plasma-derived medicinal products (PDMPs) Part I

Johannes Bluemel
Head of Viral Safety Sectiont

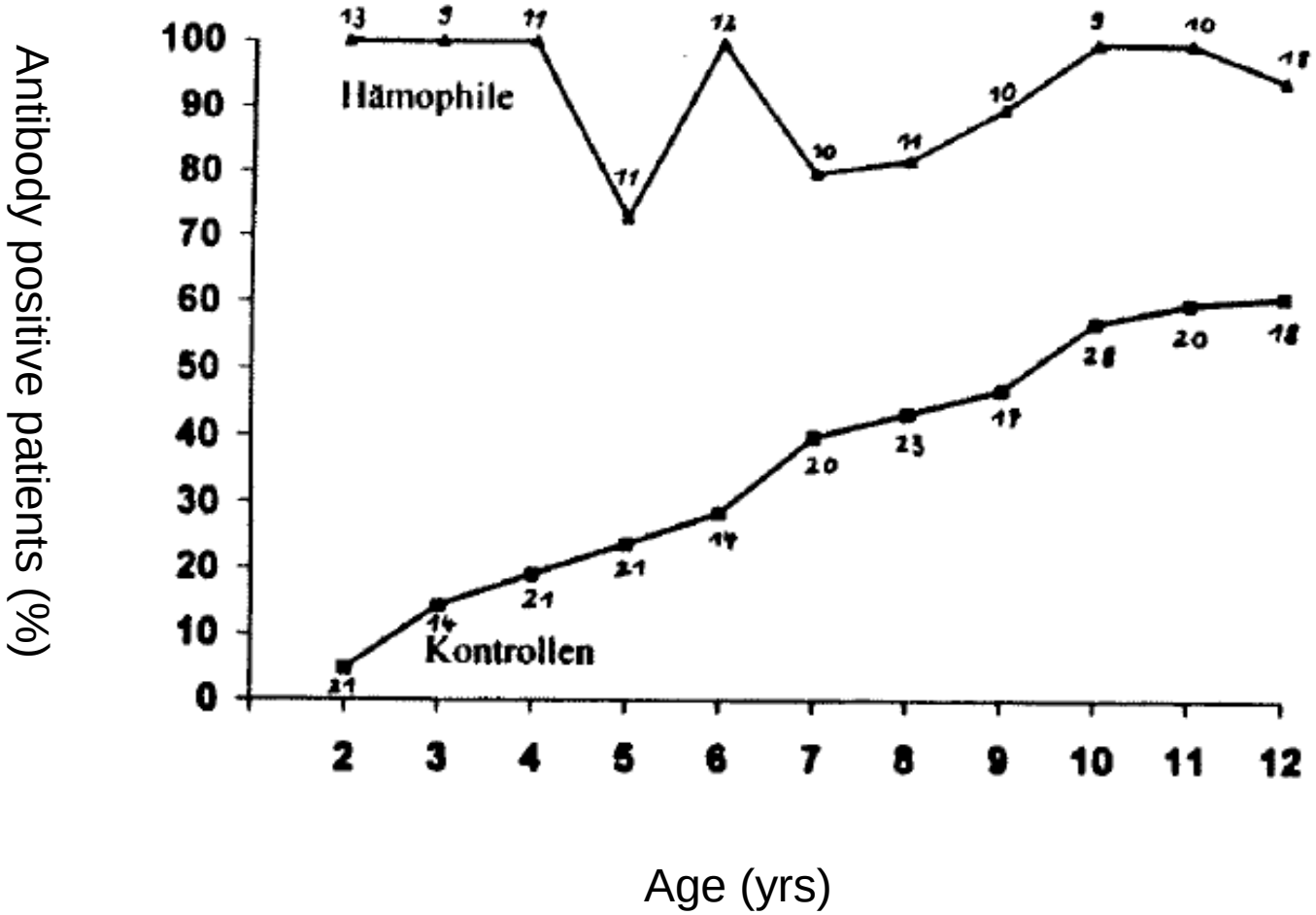
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

Paul-Ehrlich-Institut

Parvovirus B19 Prevalence in Haemophilia Patients



AM Eis-Hübinger, I Wiedemann, J. Blümel, J. Oldenburg, H.H. Brackmann, B. Matz, KE Schneeweis
25. Hämophilie Symposium 1994. https://link.springer.com/chapter/10.1007/978-3-642-79648-7_40

Mauser-Bunschoten EP, Zaaijer HL, van Drimmelen AA, de Vries S, Roosendaal G, van den Berg HM, Lelie PN. High prevalence of parvovirus B19 IgG antibodies among Dutch hemophilia patients. Vox Sang. 1998;74(4):225-7. https://onlinelibrary.wiley.com/doi/10.1046/j.1423-0410.1998.7440225.x

Soucie JM, Siwak EB, Hooper WC, Evatt BL, Hollinger FB. the Universal Data Collection Project Working Group. Human parvovirus B19 in young males with hemophilia A: associations with treatment product exposure and joint range-of-motion limitation. Transfusion. 2004; 44:1179–85 https://onlinelibrary.wiley.com/doi/10.1111/j.1537-2995.2004.04029.x

…the seroprevalence of IgG antibodies to B19V was much higher among very young (age 2 – 7 years) hemophilia patients exposed to plasma-derived products compared to those not exposed.

*…**joint range of motion (ROM) loss** was greater among subjects who were seropositive compared to those who were seronegative, suggesting that at least some of the joint disease may have resulted from B19V delivered intravenously from contaminated product.*

Table 1. Cases of plasma product associated B19V infections

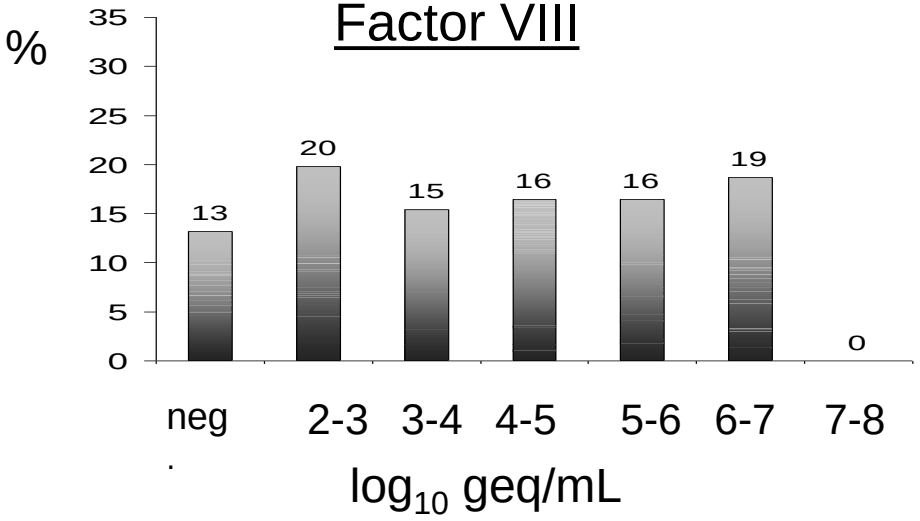
Product	Virus inactivation method	Patient, sex, age in years	Underlying disease	Symptoms	Reference
FIX	dry heat	f, 39	haemophilia B (transmitter)	exanthema, arthralgia, 19 days following i.v. drip	101
		m, 11	haemophilia B	exanthema, arthralgia, 35 days following i.v. drip	
		m, 20	haemophilia B	exanthema, fever, 12 days following i.v. drip	
FVIII	SD	m, 11	haemophilia A	hypoplastic anaemia	102
FVIII	dry heat	m, 33	mild haemophilia A, non-steroidal immuno-suppression, sulfasalazin	hepatomegaly, pancytopenia, high fever, exanthema	79
FVIII	SD or pasteurisation	m, 11	mild haemophilia A, steroidal immunosuppression	fever 12 days following i.v. drip, somnolence, confusion, pancytopenia, liver cystolysis	80
FIX	SD	f, 31	haemophilia B (transmitter)	fever, exanthema, arthralgia, lymphadenopathy 21 days following i.v. drip	103
FVIII	SD	m, 7	mild haemophilia A	aplastic crisis 16 days following i.v. drip	104
Fibrin sealant	dry heat	f, 3 cases (35–42)	cervical carcinoma, ovarial carcinoma, myoma	fever, leukopenia, erythroblast-openia, 6–11 days following administration	105
Plasma	SD	f, 36	myasthenia gravis	exanthema, arthralgia, 14 days following i.v. drip	64
Fibrin sealant	pasteurisation	m, 4 cases f, 2 cases >20	lung cancer	reticulocytopenia	106
FVIII	dry heat	m, 5	haemophilia A	asymptomatic	70
FEIBA	vapor heat	m, 1	haemophilia A	asymptomatic	70
FVIII	SD	m, 47	mild haemophilia A	fever, arthralgia, 7 days following i.v. drip	71

Arbeitskreis Blut Untergruppe, Blümel et al., *Transfus Med Hemother* (2010) 37 (6): 339–350. https://doi.org/10.1159/000322190

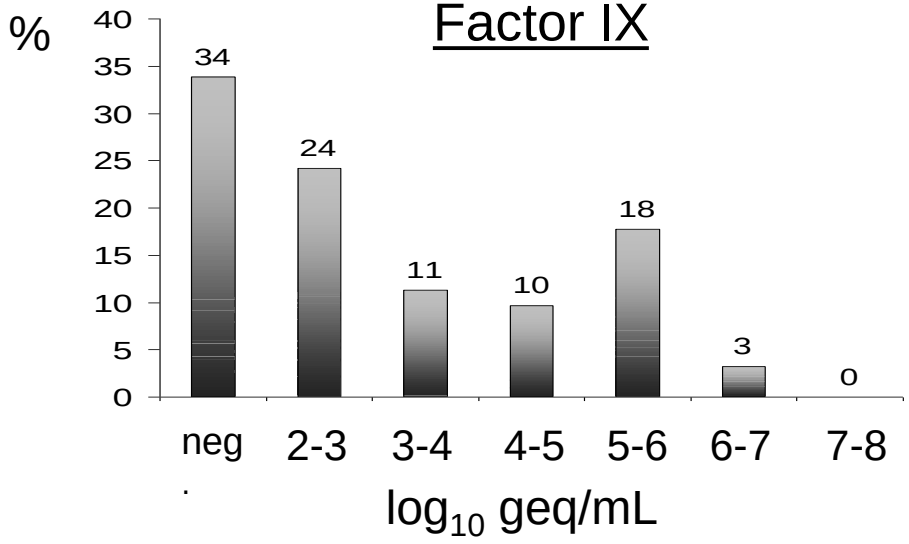
Parvovirus B19 DNA in Blood Products (PEI results)

Paul-Ehrlich-Institut

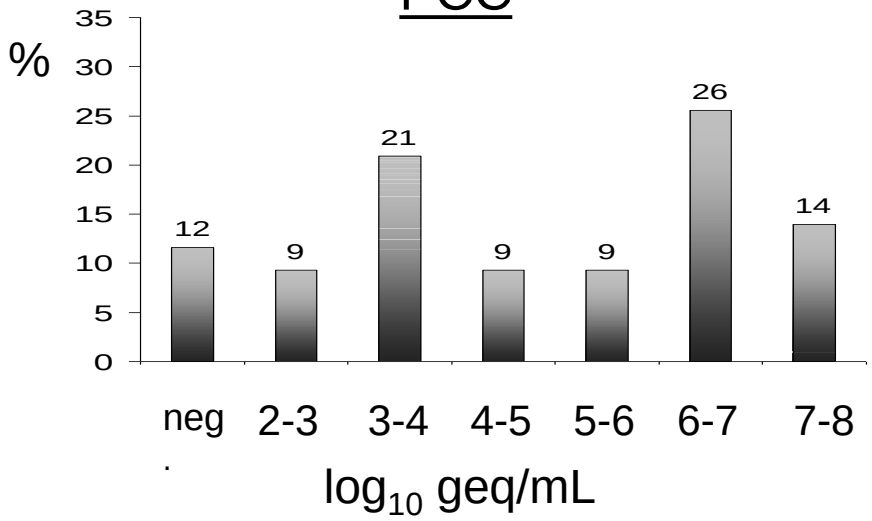
Factor VIII



Factor IX



PCC



Antithrombin III:
19% positive (<3log10 geq/mL)

Immunoglobulins and Albumin:
8% positive (<4log$_{10}$ geq/mL)

Schmidt I, Blümel J. Seitz H, Willkommen H, Löwer J. Vox Sang. 2001 Nov;81(4):228-35. doi: 10.1046/j.1423-0410.2001.00120.x

Analysis of two Transmission Cases

Two children with haemophilia A at high dose therapy

DNA sequence analysis from patients, products, and environmental B19V samples showed transmission by clotting factors

Patient A received 180 mL containing 8.6 x 10^6 geq/mL; Sum: 1.6 x 10^9 geq
Patient B received 230 mL containing 4.3 x 10^4 geq/mL; Sum: 9.9 x 10^6 geq

- Products had been manufactured from **highly-viraemic** plasma-pools (10^8 or 10^7 genomes per mL)
- The applied heat treatment (dry heat or steam heat) did not completely the inactivate the high or medium load B19V

Blümel et al., (2002). Parvovirus B19 transmission by heat-treated clotting factor concentrates Transfusion 42:1473-1481

In 2000, some manufacturers began voluntary “in process” nucleic acid test (NAT) screening of plasma pools for B19V

Where does the limit of 10^4 Parvovirus B19 genomes per ml for plasma pools come from?

Transmission Cases via (pooled) SD Plasma

19 recipients of SD Plasma containing 7.5 to 8.5 $\log_{10}$ geq/mL B10 DNA

- 7 seroconversions at 7 to 10 days
- 18 of 19 recipients seroconverted after 3 months
- 14 of 18 recipients B19 DNA positive

58 recipients of lots with virus titers between 0.5 and 3.5 $\log_{10}$ geq/mL remained seronegative.

Transcript of FDA's Blood Products Advisory Committee (BPAC) Meeting, September 1999.
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/default.htm.

FDA Guidance

(7/2009) Guidance to Industry: recommendation of < 10^4IU/ml in manufacturing pools

Guidance for Industry Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products

European Pharmacopoia

Group 6B: Introduction of a limit of 10^4 IU Parvovirus B19 DNA per ml in plasma pools for:

- Pu Eur on SD-Plasma
- Ph Eur on Anti-D-Immunoglobulin

In Europe, there is no formal requirement on plasma pools for all plasma-derived medicinal products

What about other Plasma Products in Europe ?

e.g. … a dentist considering prophylaxis/treatment for his female patient with von Willebrand's Disease …

EMA Guideline request a risk assessment considering optional Parvovirus B19 Screening as well as virus inactivation/removal steps for non-enveloped viruses.
Guideline on Pasma-Derived Medicinal Products (EMA/CHMP/BWP/706271/2010)

The outcome of the Parvovirus B19 specific risk assessment is reflected in appropriate safety/warning statements.
Note for Guidance on the warning on transmissible agents in summary of product characteristics (SPCs) and package leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03)



It is difficult to assure Parvovirus B19 safe plasma products without high-titer screening of plasma pools and without virus inactivation/removal.

THANK YOU VERY MUCH

FOR YOUR ATTENTION