

Parvovirus B19 – Implications for PDMPs

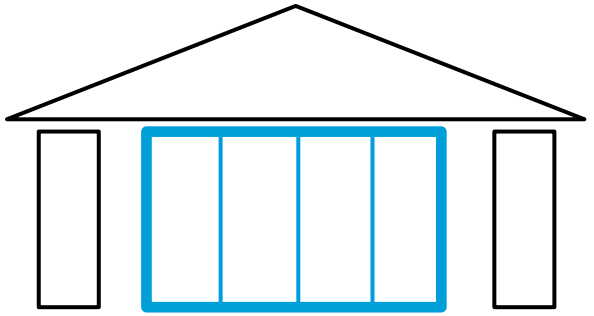
Thomas R. Kreil, Global Pathogen Safety

IPFA/PEI International Workshop on Surveillance and Screening of Blood-borne Pathogens,
May 14-15, 2025 - Heidelberg

PDMPs, and B19V Safety Margins: the „Safety Tripod“ *

- **Selection – Limited**
  - Low risk plasma donors
- **Testing – Uniquely Beneficial, due to HIGH viremia titers**
  - Plasma donations & plasma pools for confirmation
- **Reduction – Small, Non-Lipid Enveloped Virus ?**
  - Manufacturing Process Inactivation and / or Removal

    → **quantitatively DOMINANT**



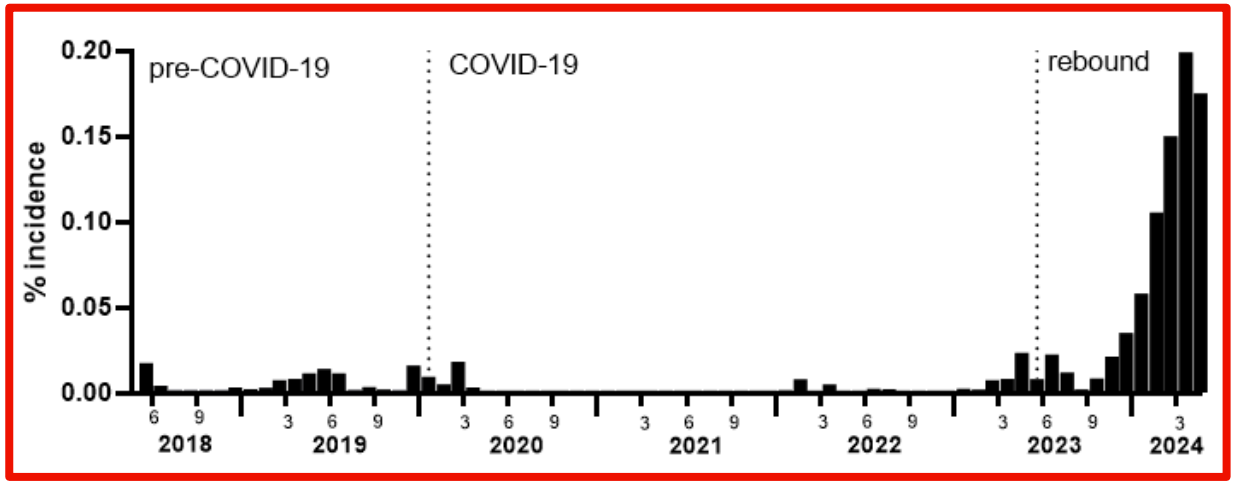
* Kreil TR, Building blocks of the viral safety margins of industrial plasma products, Annals of Blood [2018] Vol 3, No 2

Parvovirus B19 and PDMP Safety Margins

- **Rebound Outbreak**
  B19V immunization gap during the COVID-19 pandemic
  - Europe: 33-fold higher B19V incidence than average before COVID-19
  - US: 6-fold higher incidence, but still on the rise

- **B19V NAT** testing of plasma for fractionation: much more effort (!)

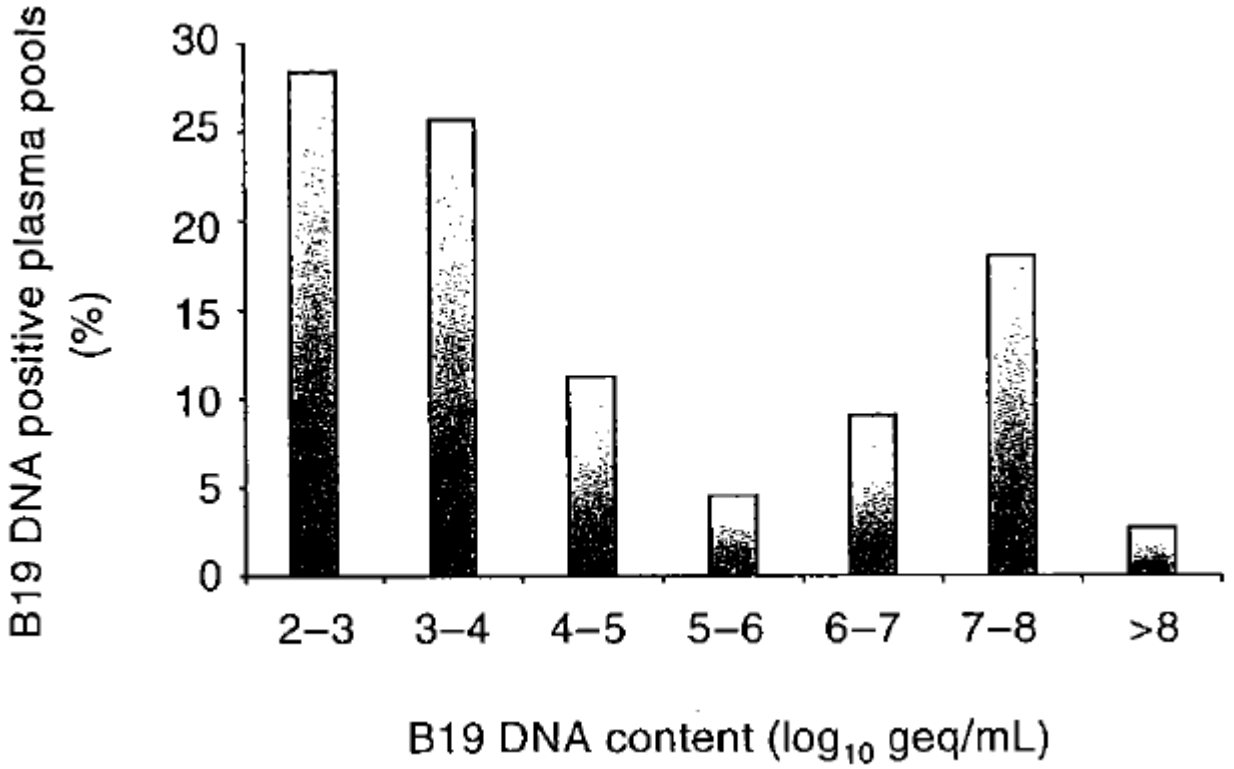
- Product **safety margins: intact**



| * Farcet, Karbiener, Aberham, Powers, Aue, Kreil.
| Parvovirus B19 rebound outbreak 2024 and implications for blood- and plasma-product safety. Transfusion [2024] 64(12): 2218

B19V Testing – due to HIGH Viremia Titers …

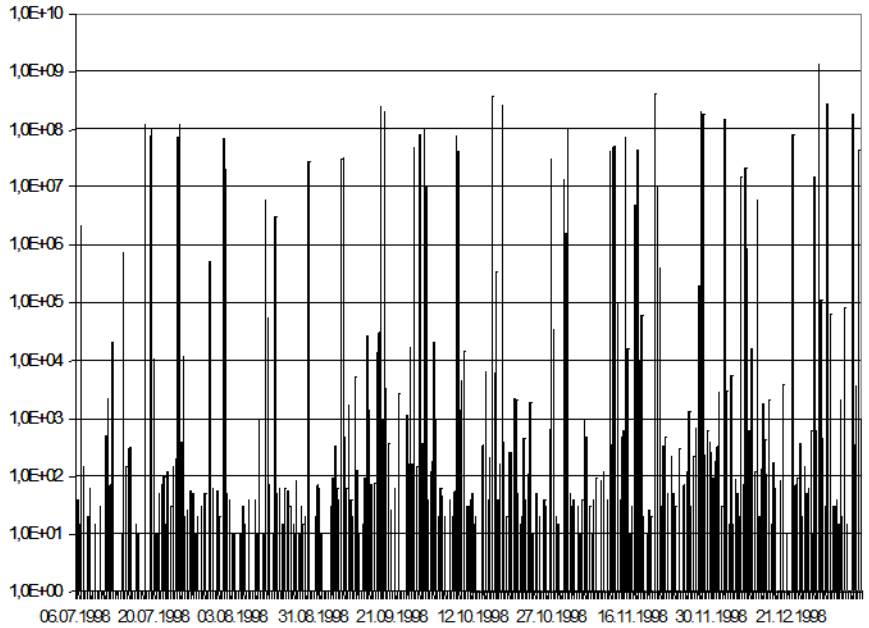
- *222 of 372 plasma pools for fractionation contained B19V at concentrations of 10^2 – 10^8 geq/ml … 35% contained >10^6 geq/ml **

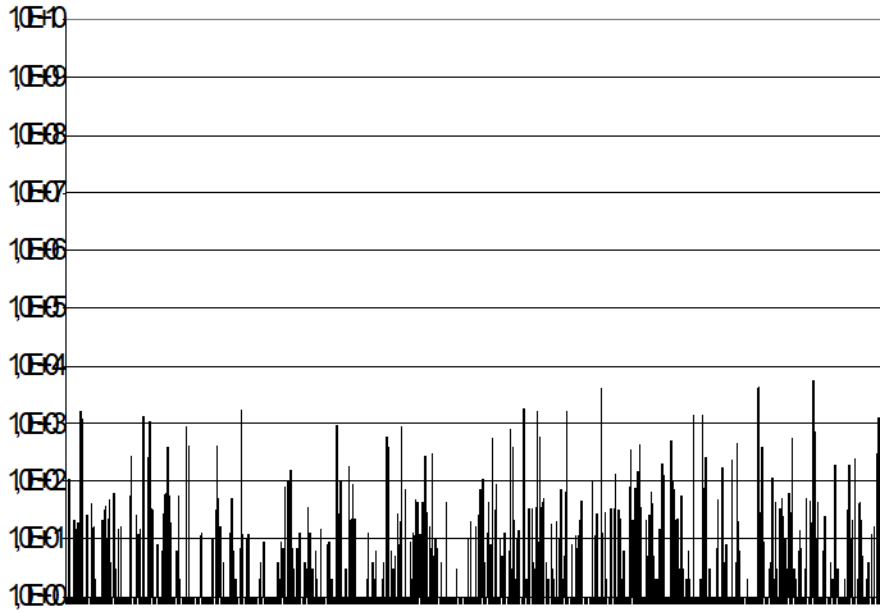


 | * Schmidt, Blümel, Seitz, Willkommen, Löwer. Parvovirus B19 DNA in plasma pools and plasma derivatives. Vox Sang [2001] Nov;81(4):228-35

B19V Testing – Uniquely Beneficial (!)

- In-process testing: marked reduction of B19V titers *
- Means: $>10^7 \rightarrow <10^2$, i.e. $>5 \log_{10}$ (!)





* S Petteway, for PPTA. Parvovirus B19 In-process Control Testing of Source Plasma. March 11, 2004 – PPTA Emerging Infectious Disease Rundtable

B19 Reduction – Small, Non-Lipid Enveloped Virus ?

Note for Guidance on Plasma-Derived Medicinal Products *

- *… viruses potentially present in plasma that are **resistant** to the inactivation/removal methods that can currently be applied to a class of product, e.g. **parvovirus B19** in coagulation concentrates.*

- *Validation studies for coagulation factors should also include an appropriate **model for the parvovirus B19**.*
  … canine, porcine, murine and bovine parvovirus …

| * CPMP/BWP/269/95, rev. 1 of Jan 2001

B19 Reduction – Small, Non-Lipid Enveloped Virus ?

- **Removal during Fractionation**
  - *… partition processes involve a large number of variables that are difficult to control and are difficult to scale down for validation purposes. **
  - Recent B19V exposure at large scale (not a welcome experience): but, **down-scale data fully predictive of large-scale** performance

    - B19V positive pool in manufacturing, Human Serum Albumin process
      Lab scale: ≥5.7
      Manufacturing scale: ≥5.1

| * Note for Guidance on Plasma-Derived Medicinal Products. CPMP/BWP/269/95, rev. 1 of Jan 2001

B19 Reduction – Small, Non-Lipid Enveloped Virus ?

- **Inactivation by Pasteurization, i.e. liquid heating for 10 hours @ 60° C**
  - Effective inactivation of B19V,
    at conditions that do not provide for inactivation of animal parvovirus models
  - Dependence on **matrix composition**, however (!)

    - Heat stability of parvovirus B19: kinetics of inactivation
      TF Schwarz … M Roggendorf, Zentralbl Bakteriol [1992] Jul;277(2):219-23
    - Inactivation of parvovirus B19 during pasteurization of human serum albumin
      J Blümel … J Löwer, Transfusion [2002] Aug;42(8):1011-8
    - Inactivation of parvovirus B19 by liquid heating incorporated in the manufacturing process of human intravenous immunoglobulin preparations.
      M Yunoki … K Ikuta, Br J Haematol [2005] Feb;128(3):401-4
    - **Variability** of parvovirus B19 to inactivation by liquid heating in plasma products.
      S Hattori, M Yunoki … K Ikuta, Vox Sang [2007] Feb;92(2):121-4

B19 Reduction – Small, Non-Lipid Enveloped Virus ?

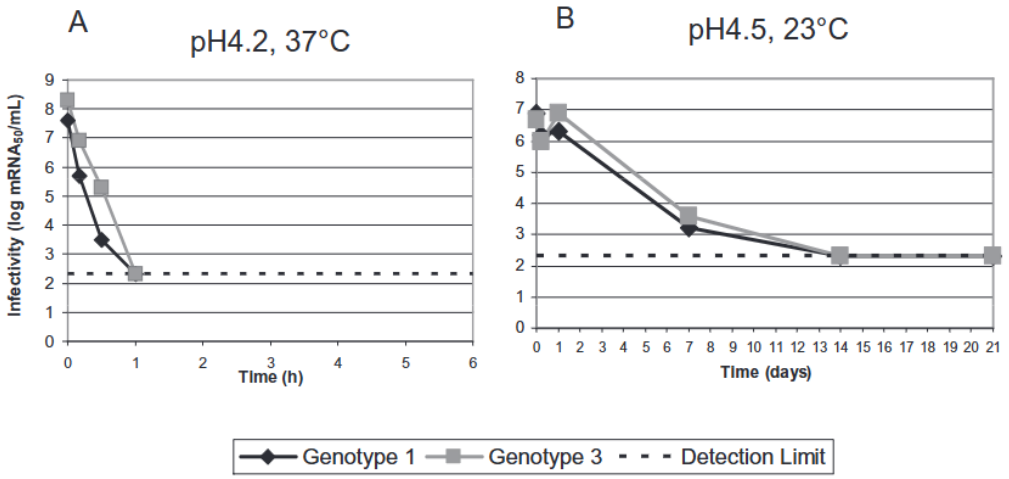
- **Inactivation by Dry Heating**
  - Different genotypes of B19V were effectively inactivated, at conditions that do not provide for inactivation of animal parvovirus models
  - Dependence on **residual moisture**, **matrix composition**, etc, however (!)

    - Evaluation of a new LightCycler reverse transcription-polymerase chain reaction infectivity assay for detection of human parvovirus B19 in dry-heat inactivation studies
      G Prikhod'ko … T Busby, Transfusion [2005] Jun;45(6):1011-9
      low moisture may stabilize
    - Inactivation of parvovirus B19 and model viruses in factor VIII by dry heat treatment at 80 degrees C
      P Roberts … J Saldana, Transfusion [2006] Sep;46(9):1648-50
      … combination of this inactivation step with additional procedures such as plasma screening for B19 by PCR, however, should ensure adequate products safety.
    - Inactivation of parvovirus B19 during STIM-4 vapor heat treatment of three coagulation factor concentrates.
      A Berting … T Kreil, Transfusion [2008] Jun;48(6):1220-6

B19 Reduction – Small, Non-Lipid Enveloped Virus ?

- **Inactivation by Low pH**
  - Different genotypes of B19V were similarly effectively inactivated, at conditions that provide less inactivation for animal parvovirus models

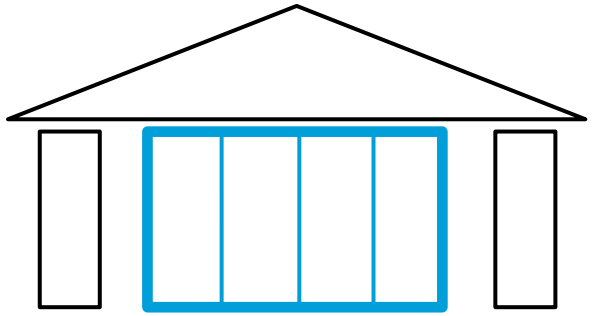
  - Inactivation and neutralization of parvovirus B19 Genotype 3
    J Blümel … S Baylis, Transfusion [2012] Jul;52(6):1490-7
    5% HSA (A), PBS (B)



PDMPs, and B19V Safety Margins: the „Safety Tripod“ *

- **Selection – Limited**
- **Testing – Uniquely Beneficial, due to HIGH viremia titers**
- **Reduction – Small, Non-Lipid Enveloped Virus ?**
  - B19V is **not similar** to other parvovirus model viruses

  →**“case-by case”, verification is needed**
- **Watch-Out (!)**
  - Next non-lipid-enveloped virus
  - High viremia titers, unclear physicochemical properties



* Kreil TR, Building blocks of the viral safety margins of industrial plasma products, Annals of Blood [2018] Vol 3, No 2

Human Circovirus – a Small, Non-Lipid Enveloped Virus

- **Epidemiology: Rare occurrence**, as far as we know for now
  - EU and China: few cases in immunocompromised patients
  - Viremia: potentially high (10^{10} gc/ml) [1]
  - No contamination detected in plasma pools for fractionation [2]
- Physicochemistry, virus reduction: not understood

→ **Verification ? TBD**

1. Circovirus Hepatitis Infection in Heart-Lung Transplant Patient, France
   P Pérot … M Eloit, EID [2023] Feb;29(2):286-293
   … >10^8 gc/g liver, concomitant with hepatic cytolysis.
2. Human Circovirus is not detected in plasma pools for fractionation *
   P Pérot … T Kreil, M Eloit, Transfusion [2024] Jan;64(1):16-18
   corresponding to more than 200.000 plasma donations … LOD 300-600 gc/ml

THANK YOU !

Any Questions ?

