

Newly Discovered Human Circovirus: Prevalence, and Level of Concern?

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Global Pathogen Safety

IPFA/PEI workshop, Aarhus, Denmark

New Human Circovirus, France / China

France

- heart-lung transplanted patient with unexplained hepatitis
- HCirV-1 detected in serum, plasma and blood
  - up to **10^{11} genome copies/mL**

→ first Circovirus with reported pathogenicity in human

→ one additonal EU case under investigation @Institut Pasteur

China

- two intravenous drug users, also positive for HIV and HCV
- HuCV2 detected in blood, sampled in 2009


EMERGING INFECTIOUS DISEASES

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Volume 29, Number 2—February 2023

Research

Circovirus Hepatitis Infection in Heart-Lung Transplant Patient, France

Philippe Pérot[1], Jacques Fourgeaud[1], Claire Rouzaud[1], Béatrice Regnault, Nicolas Da Rocha, Hélène Fontaine, Jérôme Le Pavec, Samuel Dolidon, Margaux Garzaro, Delphine Chrétien, Guillaume Morcrette, Thierry Jo Molina, Agnès Ferroni, Marianne Leruez-Ville, Olivier Lortholary[2], Anne Jamet[2], and Marc Eloit[2]


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Volume 29, Number 5—May 2023

Dispatch

Unknown Circovirus in Immunosuppressed Patient with Hepatitis, France, 2022

Christophe Rodriguez, Laure Boizeau[1], Alexandre Soulier[1], Melissa N'Debi, Vanessa Demontant, Elisabeth Trawinski, Sarah Seng, Hélène Fontaine, Paul-Louis Woerther, Sarah Marchand, Slim Fourati, Stéphane Chevaliez, Pierre Cappy, Stanislas Pol, and Jean-Michel Pawlotsky

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EMERGING INFECTIOUS DISEASES

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Volume 29, Number 5—May 2023

Dispatch

Novel Circovirus in Blood from Intravenous Drug Users, Yunnan, China

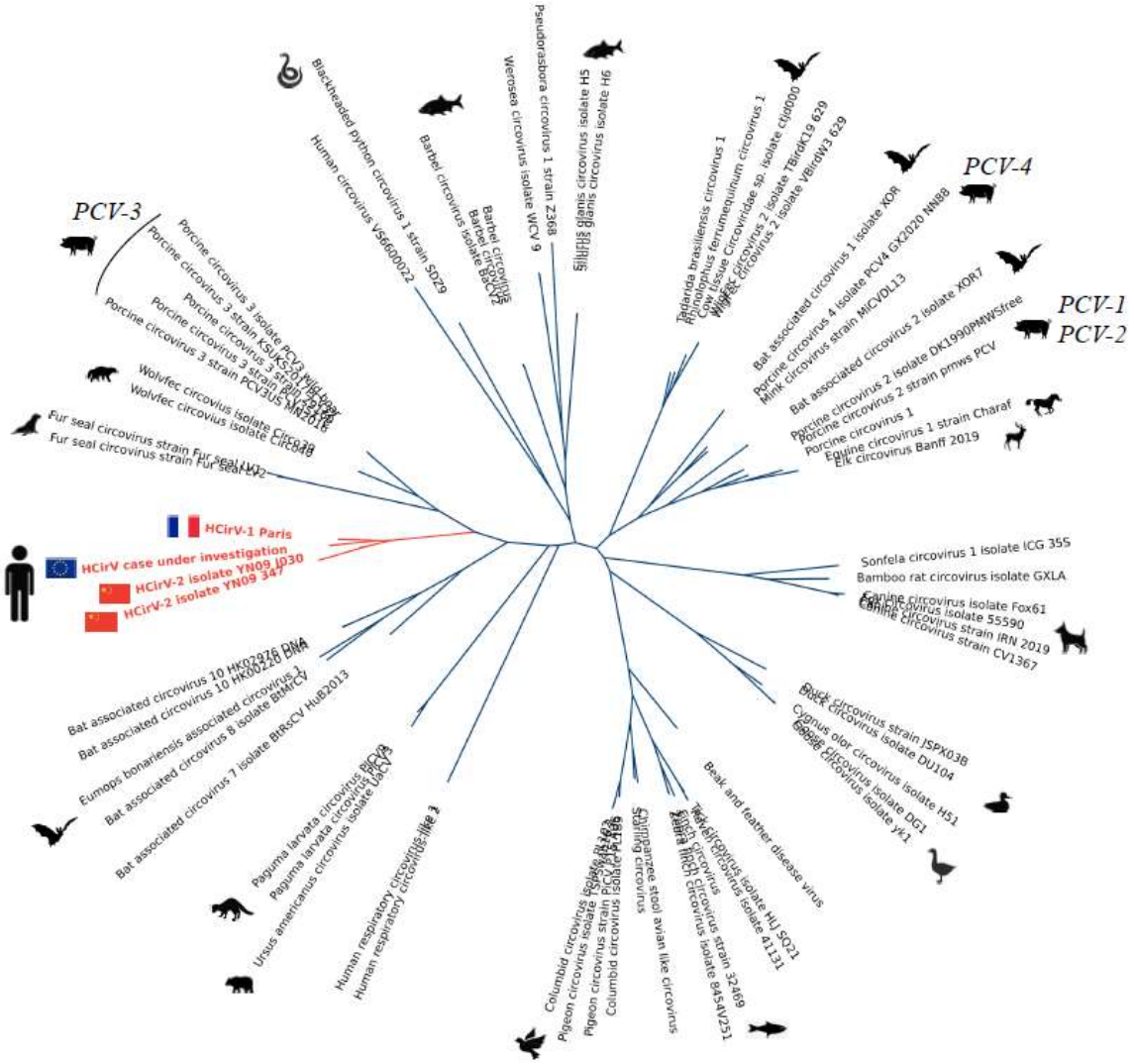
Yanpeng Li, Peng Zhang, Mei Ye, Ren-Rong Tian, Na Li, Le Cao, Yingying Ma, Feng-Liang Liu, Yong-Tang Zheng, and Chiyu Zhang

Author affiliations: Fudan University, Shanghai, China (Y. Li, P. Zhang, L. Cao, Y. Ma, C. Zhang); Chinese Academy of Sciences, Kunming, China (M. Ye, R.-R. Tian, N. Li, F.-L. Liu, Y.-T. Zheng); Kunming Medical University, Kunming (N. Li)

New Human Circovirus

Virus

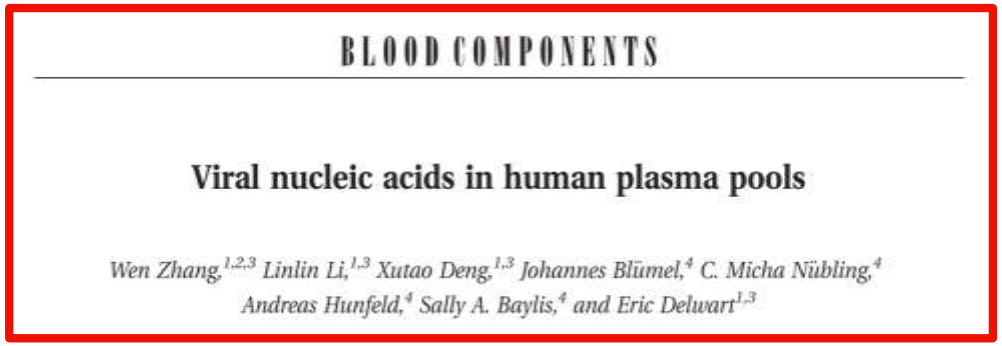
- small: 17-22 nm
- non-lipid enveloped (NLE)
  ~ difficult to inactivate
- phylogenetically related to PCV-3
- origin unknown
  - already circulating in population ?
  - zoonosis, occasionally transmitted from animal to human?
  - favored by an immune compromise?



New Human Circovirus – prevalence ?

- NGS analysis of plasma manufacturing pools
  - sourced 1998-2001
  - US & EU

  → no HCirV-like sequences reported


BLOOD COMPONENTS

Viral nucleic acids in human plasma pools

Wen Zhang,[1,2,3] Linlin Li,[1,3] Xutao Deng,[1,3] Johannes Blümel,[4] C. Micha Nübling,[4] Andreas Hunfeld,[4] Sally A. Baylis,[4] and Eric Delwart[1,3]

- NGS analysis of plasma pools
  - collected 2018-2019
  - healthy Chinese blood donors

  → few *Circoviridae* sequences identified, no match to specific viral sequences


Virus Research 323 (2023) 199004

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Virus Research

journal homepage: www.elsevier.com/locate/virusres

ELSEVIER

An atlas of the blood virome in healthy individuals

Bo Feng[a,1], Bo Liu[a,1], Min Cheng[b,1], Jie Dong[a], Yongfeng Hu[a,*], Qi Jin[a,*], Fan Yang[a,*]

- Moustafa et al., 2017 – The blood DNA virome in 8,000 humans → no *Circoviruses* identified
- Tisza et al., 2020 – Discovery of several thousand highly diverse circular DNA viruses → Circovirus in cow, fruitfly, minnow but not in human blood

New Human Circovirus – prevalence ?

GPS & Institut Pasteur Pathogen Discovery Laboratory

- Evaluation of prevalence and titer in plasma pools before fractionation
  - 48 plasma pools
    - mini pools of ~100 dontations
    - large pools of ~10,000 donations
  - main plasma sourcing geographies: US, EU and Japan
  - qPCR @ Institut Pasteur
    ~ HCirV-1 specific
    ~ HCirV-1 + HuCV2 specific

New Human Circovirus – prevalence ?

GPS & Institut Pasteur Pathogen Discovery Laboratory

- **no traces** of HCirV sequences,
  in any of the pools tested

  – ~ 200,000 plasma donations
  – 100 to 10,000-fold dilution of individual donations
  – LOD of qPCR 300-600 gc/mL

  → high level of viremia is a rare event
  → potentially low, transient or variable viremia in healthy plasma donors (?)



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BRIEF REPORT

TRANSFUSION

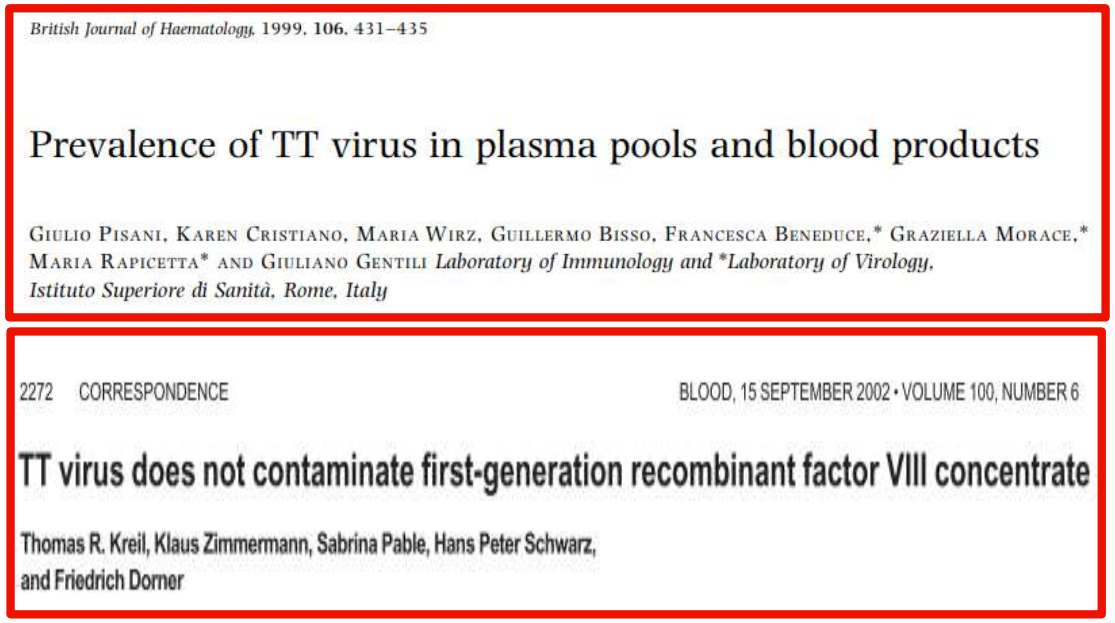
Human Circovirus is not detected in plasma pools for fractionation

Philippe Pérot[1,2] | Nicolas Da Rocha[1,2] | Maria R. Farcet[3] | Thomas R. Kreil[3] | Marc Eloit[1,2,4]

New Human Circovirus – Model Viruses

- **Torque Teno Virus** (Human Circovirus)

- small (~30 nm), NLE
- non-pathogenic in humans
- high prevalence
  ~82% of plasma donations
- low viral load in plasma pools
  (200-500 copies/mL)



British Journal of Haematology, 1999, **106**, 431–435

Prevalence of TT virus in plasma pools and blood products

GIULIO PISANI, KAREN CRISTIANO, MARIA WIRZ, GUILLERMO BISSO, FRANCESCA BENEDUCE,* GRAZIELLA MORACE,* MARIA RAPICETTA* AND GIULIANO GENTILI *Laboratory of Immunology and *Laboratory of Virology, Istituto Superiore di Sanità, Rome, Italy*

2272 CORRESPONDENCE BLOOD, 15 SEPTEMBER 2002 • VOLUME 100, NUMBER 6

TT virus does not contaminate first-generation recombinant factor VIII concentrate

Thomas R. Kreil, Klaus Zimmermann, Sabrina Pable, Hans Peter Schwarz, and Friedrich Dorner

→ clearance to below PCR LOD during Human albumin manufacture

New Human Circovirus – Model Viruses

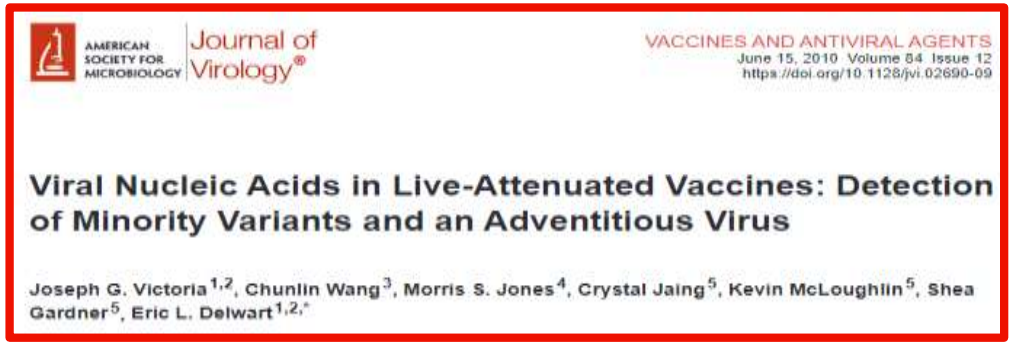
Porcine Circovirus-1, -2, -3, -4

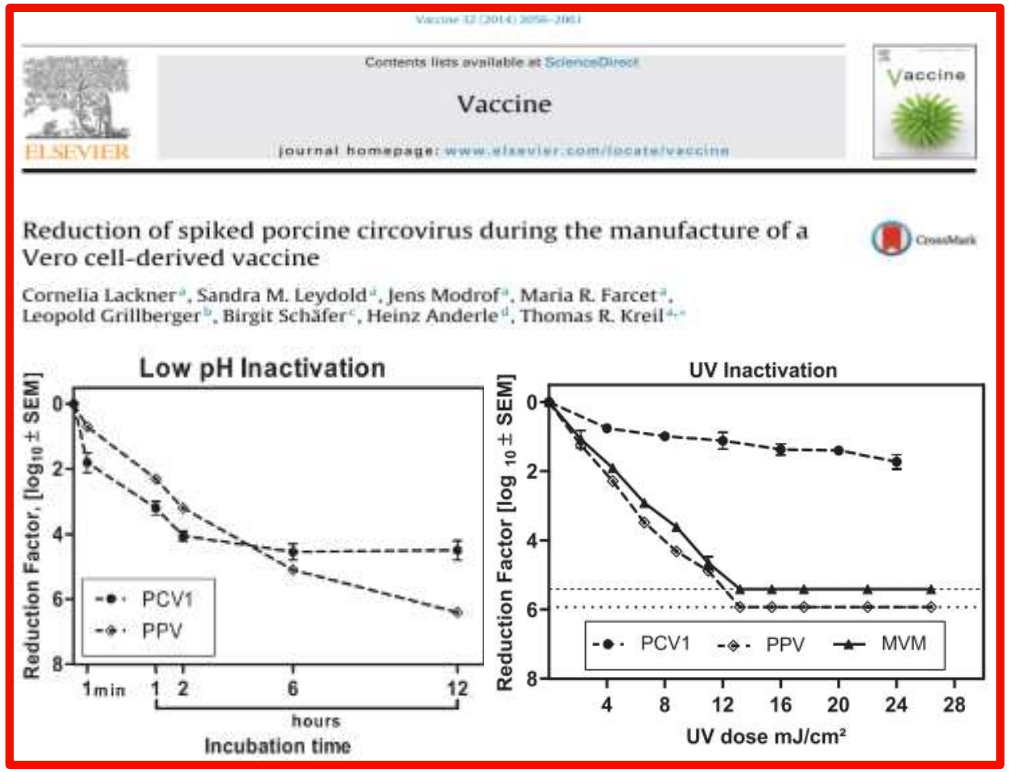
- small (~17 nm), NLE
- non-pathogenic in humans
- zoonotic potential (e.g. wild boar > tiger) [1]

Parvoviruses

- small (21-26 nm), NLE
- B19V, PPV, MMV

→ PCV-1 inactivation vs. Parvovirus models ?





| [1] Cui et al., Virus diversity, wildlife-domestic animal circulation and potential zoonotic viruses of small mammals, pangolins and zoo animals. Nature Communications 2023,14:2488

New Human Circovirus – Model Viruses

Parvovirus B19 & human plasma-derived products

→B19V vapour heat inactivation >> MMV

→B19V low pH inactivation >> MMV

Inactivation of parvovirus B19 during STIM-4 vapor heat treatment of three coagulation factor concentrates

Andreas Berting, Jens Modrof, Ulrike Unger, Matthias Gessner, Andreas Klotz, Gerhard Poelsler, and Thomas R. Kreil

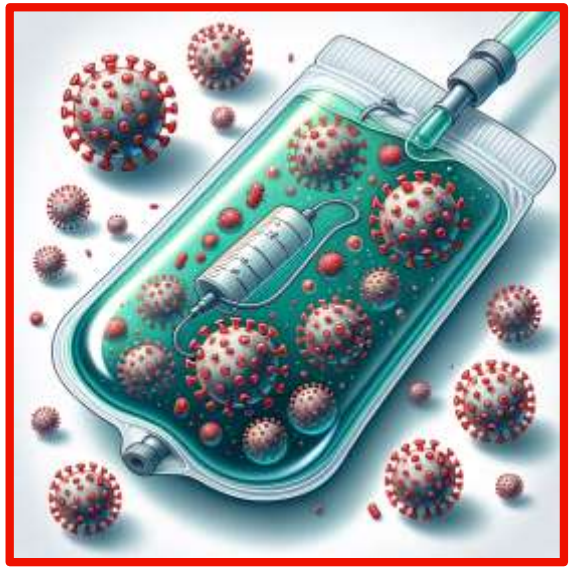
Different susceptibility of B19 virus and mice minute virus to low pH treatment

Nicola Boschetti, Isabel Niederhauser, Christoph Kempf, Albert Stühler, Johannes Löwer, and Johannes Blümel

New Human Circovirus – Model Viruses

Parvovirus B19 & human plasma-derived products

- qPCR testing to a limit of 10^4 IU B19V DNA per mL plasma pool
  - no reported B19V transmission
  - B19V sufficiently cleared in manufacturing process



New Human Circovirus – level of concern

- high level viremia is a rare event
- virus infectivity << qPCR titer
- nanofiltration with 19nm filters removed 2.2 log of PCV-1 [1]
- anion exchange chromatography – good capacity to remove PCV-1 [2]
- no information on HCirV neutralizing antibodies in plasma pools
  - indication of seroprevalence
  - possible contribution to clearance

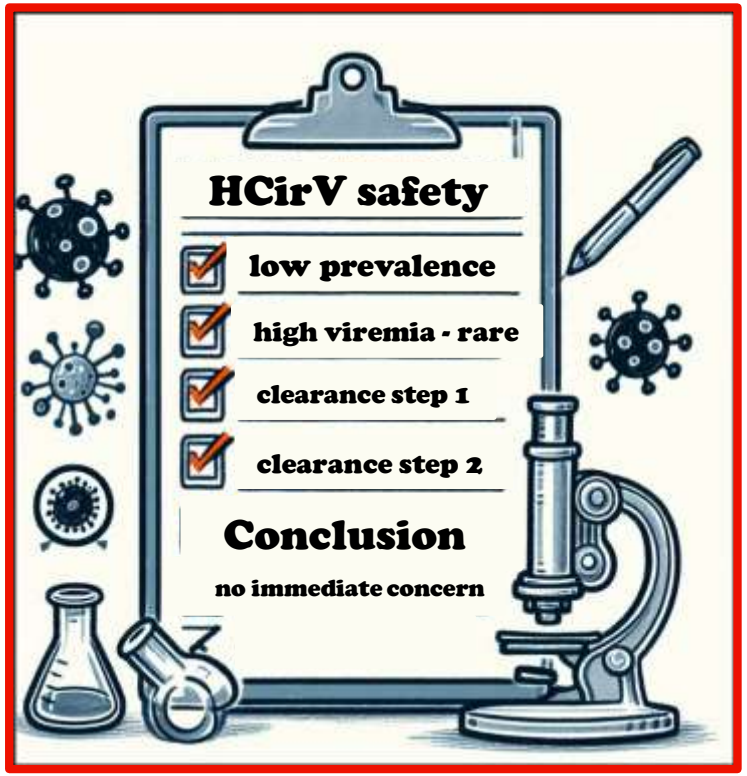
| [1] Bao et al., Successful removal of porcine parvovirus-1 from immunoglobulin G formulated in glycine solution using nanofiltration. Biologicals 2018,51:32-36
| [2] Yang et al., Porcine circovirus (PCV) removal by Q Sepharose fast flow chromatography. Biotechnol Prog 2019,29:1464-1471

New Human Circovirus, prevalence and level of concern

Summary

- no evidence of circulation in healthy plasma donor population
  - US, EU and Japan

- max. HCirV load of 300-600 gc/mL → sufficient clearance
  - previously shown for TT virus @similar levels
  - no reported transmission for B19V @ max. 10^4 IU/mL



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