

# Emerging Issues and Threats for PID Patients

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# The World Needs Plasma



## PPTA Mission Statement

The mission of PPTA is to promote the ...

- **availability** of and access to
- **safe and effective** plasma protein therapeutics for
- **all patients** in the world.

## Challenge

- *If we really want to focus on **ALL** patients in the world then all regions in the world need to collect **MORE** quality plasma. \**

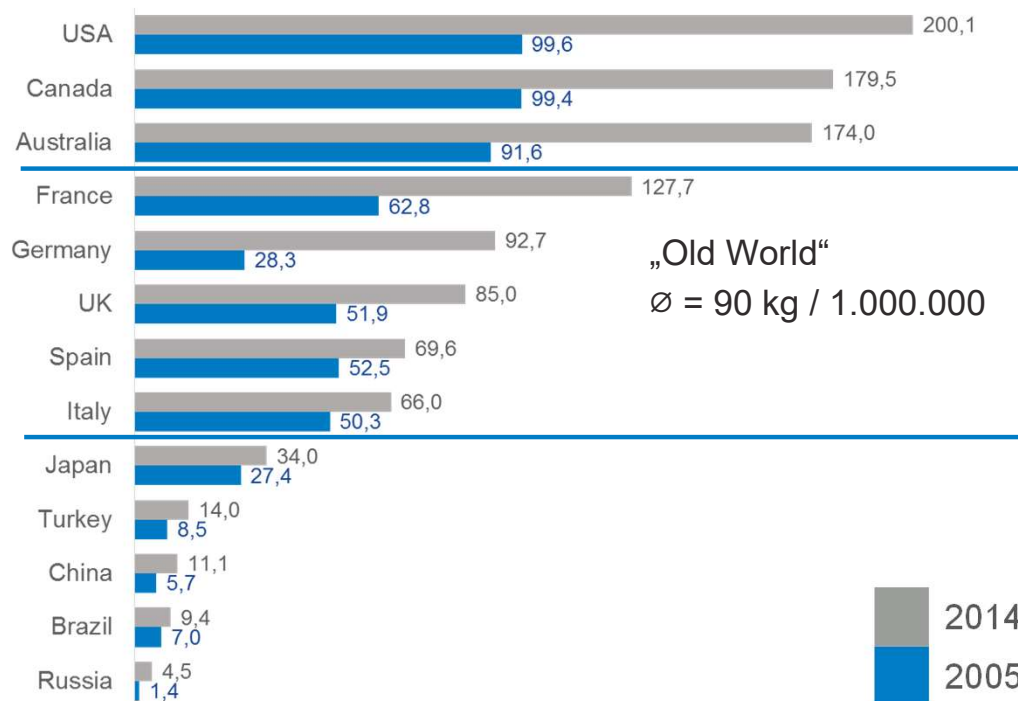
\* Jan M. BULT, PPTA  
March 13, 2018 - IPPC



# Emerging Need

## IG Use in Selected Countries \*

- IV & SC
- kg / million



\* Jan M. BULT, PPTA  
March 13, 2018 – IPPC  
→ data from  
Marketing Research Bureau

# The World Needs MORE Plasma: From Where ?

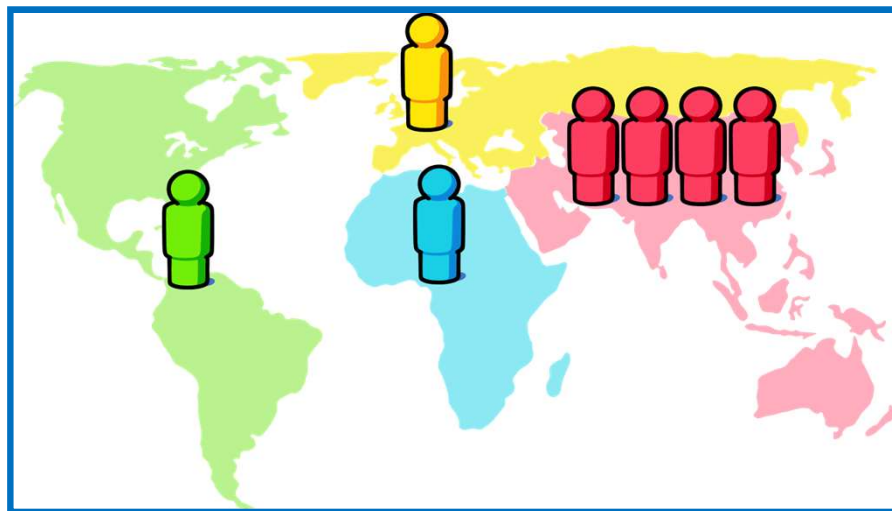
## Status 2015

- **>80% of all Plasma is Donated by <1 bio Population**

- North America 327 mio
- European Union 513 mio

- **China: Growing ...**

GapMinder,  
World Population 2015



## Four Questions \*

- Can the World continue to rely on the **United States for the primary supply** of source material for Plasma Protein Therapies?
- What is **Europe's responsibility** to provide sufficient raw material for therapies used by its citizens?
- What are the **responsibilities of other regions** to provide sufficient raw material?
- Should we move from **national** through **regional** to **global** thinking?

\* Jan M. BULT, PPTA  
March 13, 2018 – IPPC / The Source, [2018] Summer: 7

→ after David Bell, Grifols

## Emerging Need → Issues and Threats

### From the US, to Europe and Other Regions: Differences

- **Threats**

- Epidemiology**

- Known, unknown  
and emerging viruses

- **Issues**

- Antibody Spectrum**

- Different / more broad,  
but little investigated &  
understood

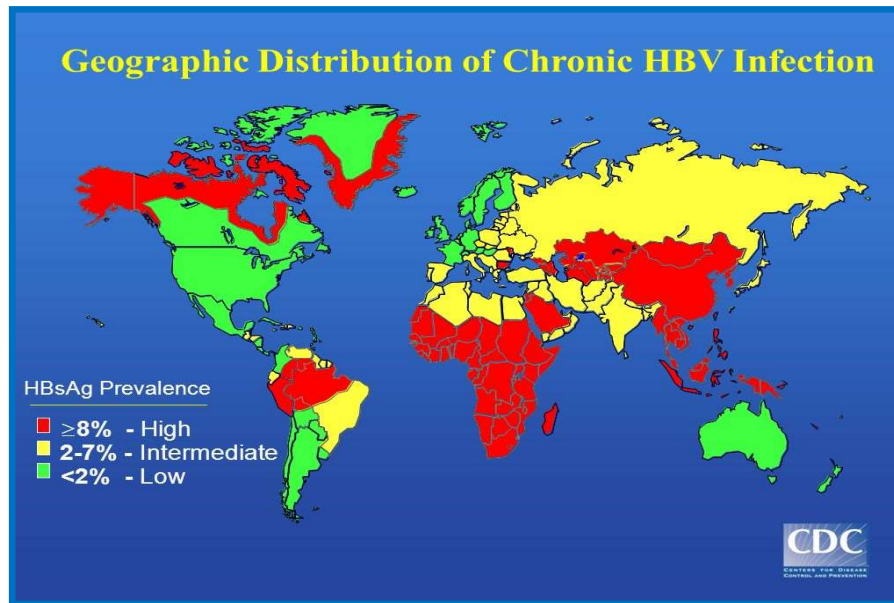


# Emerging Threats – Epidemiology

## Known viruses: Hepatitis B Virus

- Quite different levels of circulation  
(and **NOT a lot of green ...**)
- BUT: mature testing  
algorithms implemented

Hepatitis B Virus , CDC:  
Dr R V S N Sarma., M.D.,

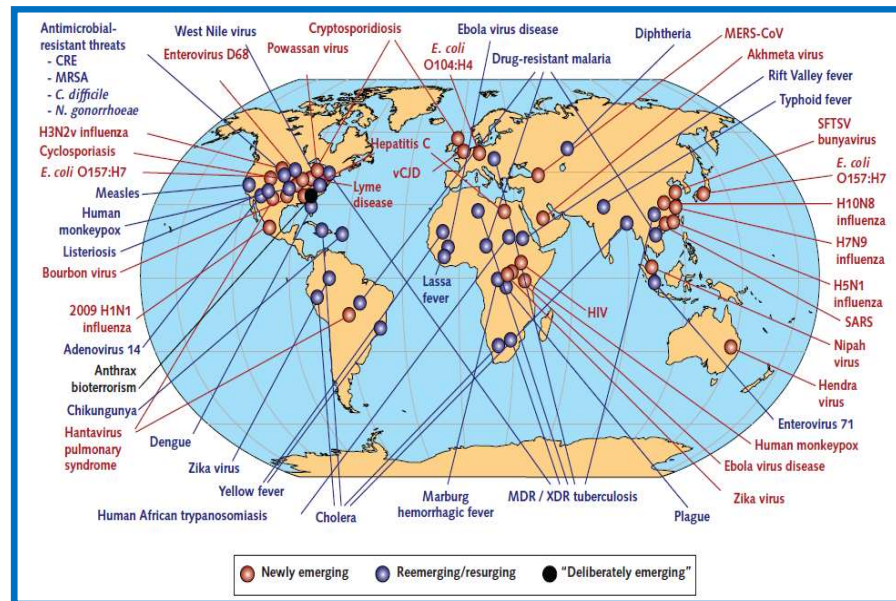


# Emerging Threats – Epidemiology

## Unknown / emerging viruses

- Continue to challenge product safety margins, accelerated by global trade and traffic
- Donor Selection, Donation Testing: of limited value ...

Paules,... Fauci  
Ann Int Med [2017] 167: 805





# Guideline on Plasma-Derived Medicinal Products

## 9. Assessing the Risk for Virus Transmission

- Estimation of potential virus particles in the finished product, N

$$N = c \times V \div R$$

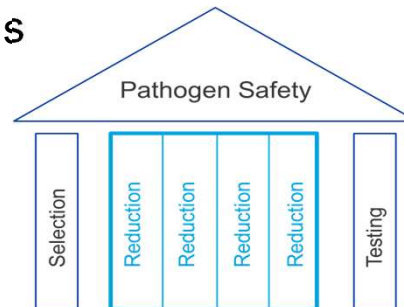
- c: potential virus concentration in the plasma pool
- V: volume of plasma required to produce one vial of product
- R: virus reduction factor obtained from validation studies

EMA/CHMP/BWP/706271/2010

# Emerging Threats – Verification (!)

## Efficacy of Virus Reduction

- West Nile Virus
- H5N1 Influenza Virus
- Chikungunya Virus
- Hepatitis E Virus
- Zika Virus



**TRANSFUSION**

**West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data**

*Thomas R. Kreil, Andreas Berting, Otfried Kistner, and Johanna Kindermann*

**H5N1 influenza virus and the safety of plasma products**

*T.R. Kreil, U. Unger, S.M. Orth, G. Petutschnig, O. Kistner, G. Poelsler, and A. Berting*

**Chikungunya virus and the safety of plasma products**

*Sandra M. Leydold,\* Maria R. Farcet,\* Johanna Kindermann, Jens Modrof, Gerhard Pölsler, Andreas Berting, M. Keith Howard, P. Noel Barrett, and Thomas R. Kreil*

**Hepatitis E virus and the safety of plasma products: investigations into the reduction capacity of manufacturing processes**

*Maria R. Farcet, Cornelia Lackner, Gerhard Antoine, Phillip O. Rabel, Andreas Wieser, Andreas Flicker, Ulrike Unger, Jens Modrof, and Thomas R. Kreil*

**Zika virus is not thermostable: very effective virus inactivation during heat treatment (pasteurization) of human serum albumin**

*Maria R. Farcet and Thomas R. Kreil*

# Emerging Issues → Antibody Spectrum ?

## (1) Exposure      (2) Geography      (3) Manufacturing Process

→ Immunization  
→ Infection

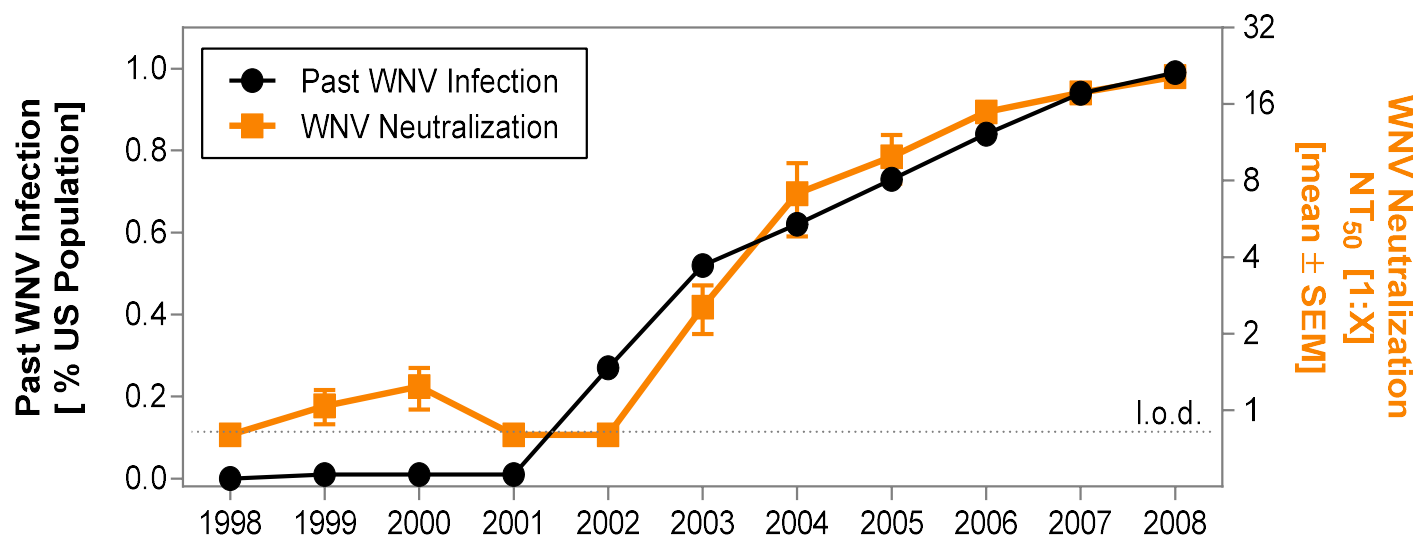
→ EU  
→ US

→ Enzymes (?)



# Antibody Spectrum, and Changes

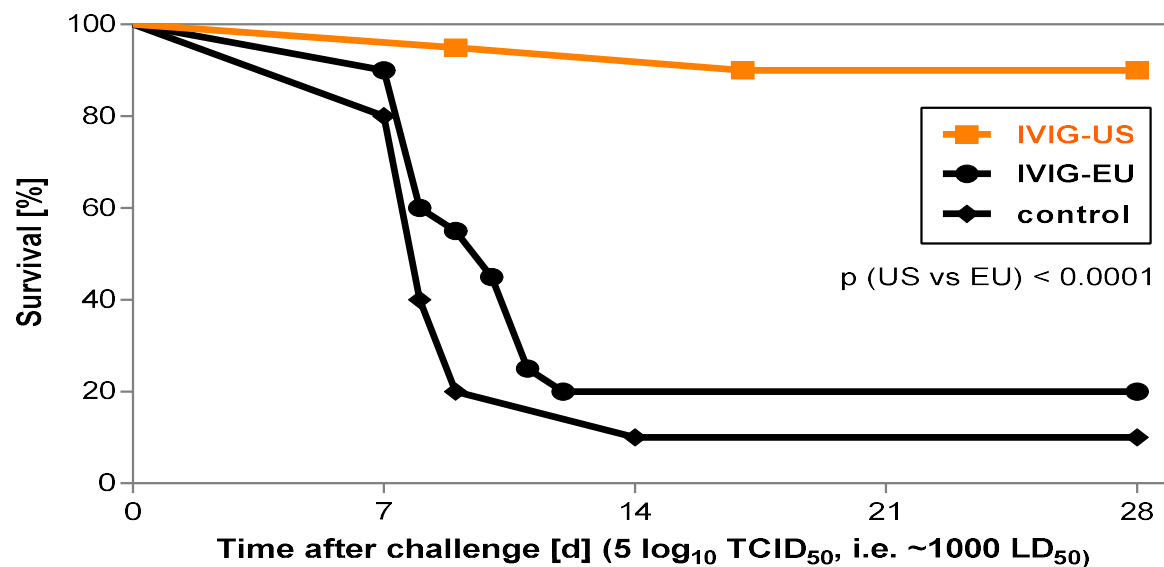
## Incidence → Seroprevalence: West Nile Virus (WNV) in the US



Planitzer CB ... Kreil TR, Emerg Infect Dis [2009] 15(10):1668-1670

# Antibody Spectrum, and NEW Protection

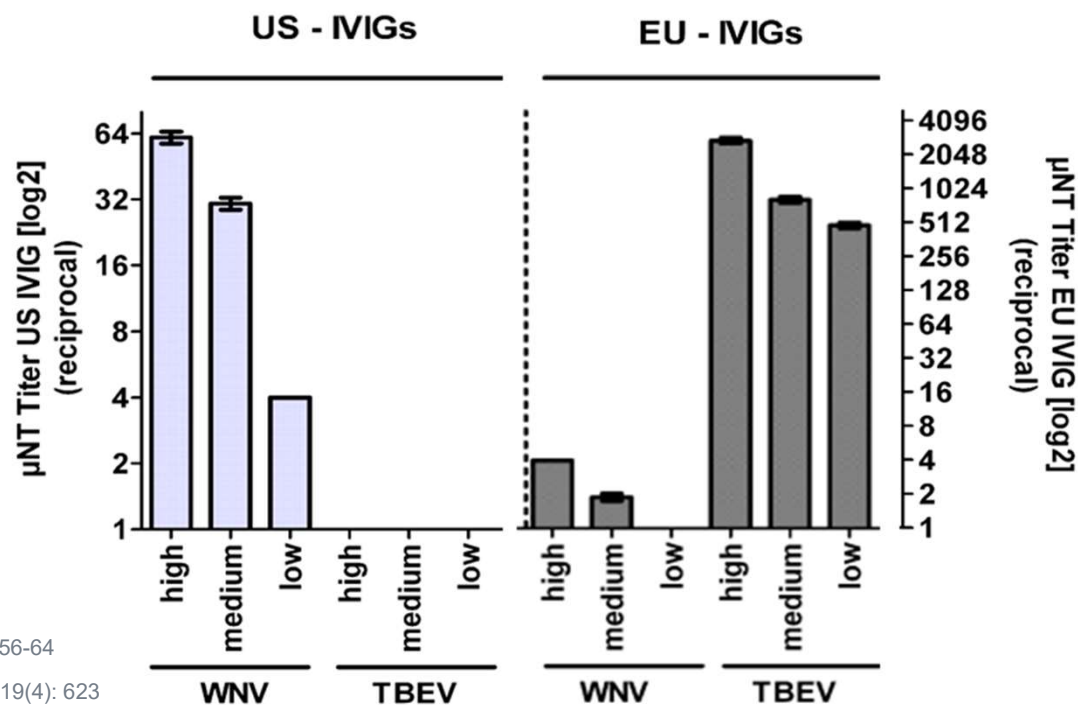
## IG Protection against WNV; mostly IgG1-mediated



Planitzer ... Kreil, J Infect Dis [2007] 196(3):435-440  
Hofmeister ... Kreil, J Virol [2011] 85(4): 1896-1899

# Antibody Spectrum: Differences ...

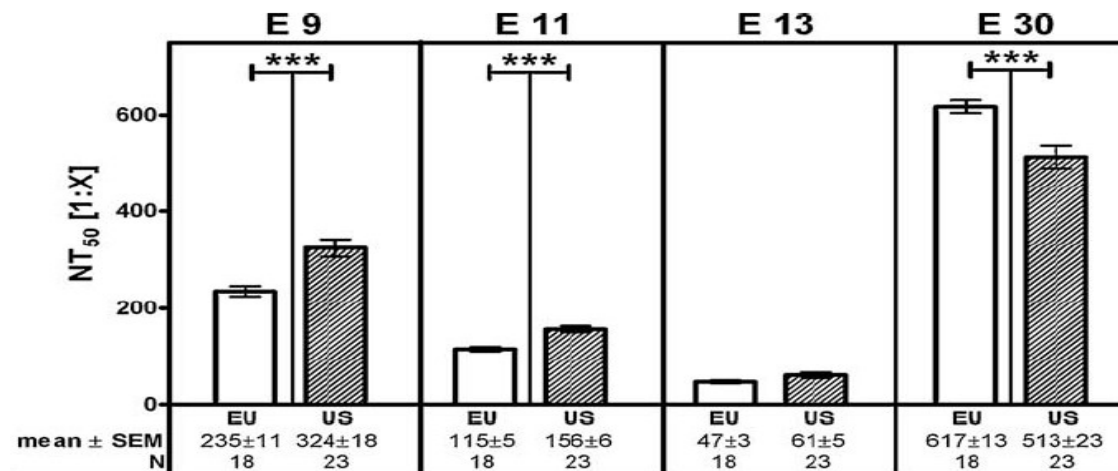
## WNV – US; Tick-Borne Encephalitis Virus (TBEV) – EU



Orlinger ... Kreil,  
J Infect Dis [2011] 203::1556-64  
Rabel ... Kreil,  
Clin Vacc Immunol [2012] 19(4): 623

# Antibody Spectrum: ... and Similarities

## Echovirus Serotypes: Minor Differences

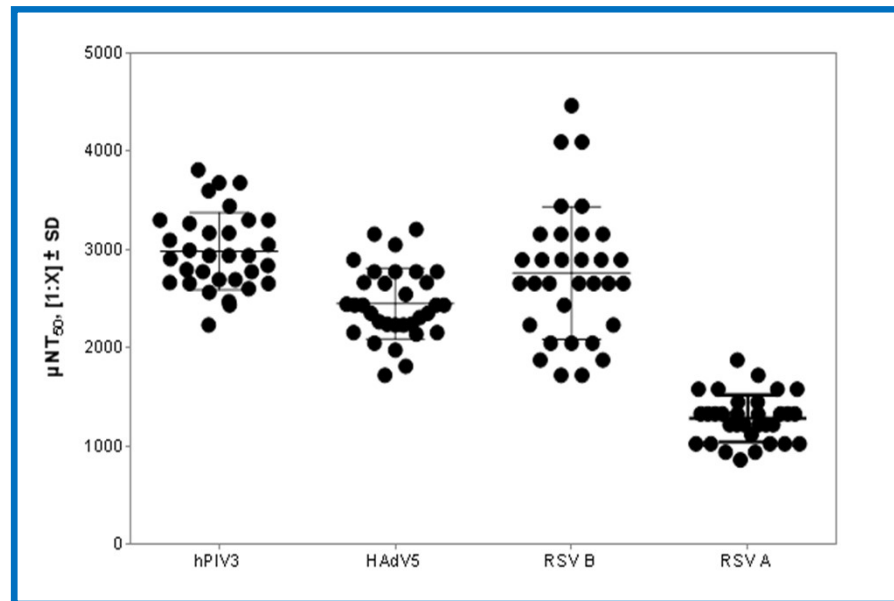


Planitzer ... Kreil, J Med Virol [2011] 83: 305-10

# Antibody Spectrum: Future Work

## IG Lots Specific Antibody Titers for Lot Release: Which ?

- Traditional: US CFR, Polio & Measles
- Future: TBD
  - IDF – FDA – PPTA
  - Nov 8-9, 2018 / DC
    - Parainfluenza Virus
    - Adenovirus
    - Respiratory Syncytial Virus



Kreil & Farcet, Transfusion - submitted



# Antibody Spectrum: What ? Where ? How Much ?

Lots of Uncharted Territory ...



# Summary

## MORE Plasma → NEW Plasma Sourcing Locations

- **Epidemiology**

of viruses may be different,

for known and unknown / emerging agents:

→ **REDUCTION Capacity**, and **VERIFICATION of Safety Margins**

- **Antibody Spectrum**

could become more diverse,

a potentially beneficial change

→ **Better Understanding Needed**



## Summary – Declining Titers

- **Hepatitis A Virus**

- Antibody titers in IVIG remain **protective**



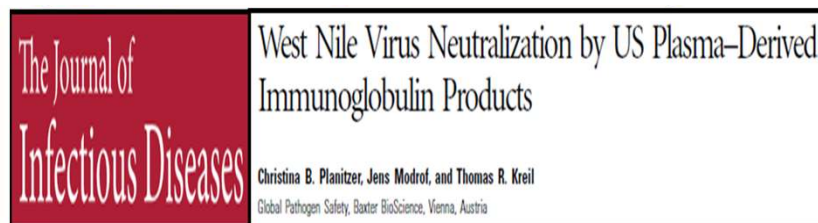
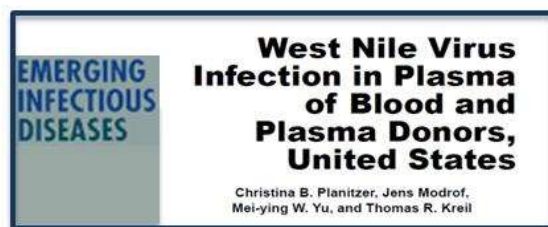
- **Measles**

- Antibody titers in IVIG remain **protective**

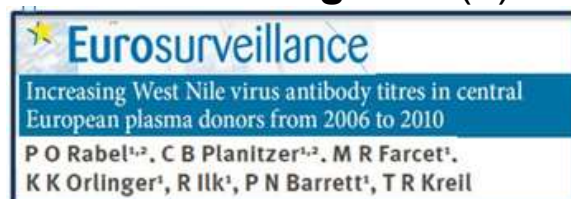


## Summary – Emerging Titters

- **West Nile Virus**
  - WNV seroconversion



- **West Nile Virus**
  - Predict **emergence** (?)
  - May elucidate **IG subclass functions**



- **Epidemics: Enterovirus D68 ?**

# Fluctuating Titers

- **Echoviruses**

