
بسم الله الرحمن الرحيم

Introduction

- Transfusion medicine is a significant young field, which has been developed in the second half of the last century.
- After the starting of the blood transfusion in the early 1940s, various transfusion associated problems have been associated.
- Transfusion transmitted infections (TTI) was first noted in late 1940s.

Bloodborne or Transfusion Transmitted Infections History

- Transfusion safety had been challenged in France, in the late 1980s, when previously cryoprecipitate (gained from 3-4 donors) based hemophilia treatment was switched to plasma derived concentrates (gained from hundreds or thousends of donors per batch).
- These multidonor based plasma derived factor derivatives proved to be very efficient bleedingwise, however, the early period shortcomings of donor screening and inactivation resulted in a large tragical series of HIV-AIDS and hepatitis C viral infections.

Bloodborne or Transfusion Transmitted Infections History

- These tragic events gave a push to quickly develop powerful new donor screening and inactivation procedures, including

➢ donor interviewing (sexual and traveling habits, social surroundings, previous medical history, drugs,etc.),

➢ new viral screening, including

✓ NAT methods,

➢ PCR and conforming community regulations like FDA or European regulatory agencies [1-3].

Bloodborne or Transfusion Transmitted Infections History

- New series of inactivation methods had been implemented including

➢heat-dry methods,

➢solvent-detergent approach,

➢affinity chromatography,

➢ later on nanofiltration, and

➢switch toward as much as possible leukodepleted products, the general standard became to apply at least minimally two approach for inactivation [1-3].

Bloodborne or Transfusion Transmitted Infections History

- These interventions resulted in much better transfusion safety pretty soon, and seemingly minimalised blood borne infections issue.
- As new or newly recognised agents started to spread, it became more and more evident, that the aforementioned donor safety and inactivation seems to fail in some instances [3,4].
- Traditional methods could not stop the prions, too, but this paper does not deal with prion issue, as it is not a cenventional pathogen.

Bloodborne or Transfusion Transmitted Infections History

- **Zika (Zyka) and Ebola Virus:**

  Much frightened pathogens, both can be transmitted by transfusion.

- **FDA implemented Zika donor screening quite recently (in endagered donor population) and the fith donor proved to be positive [18].**

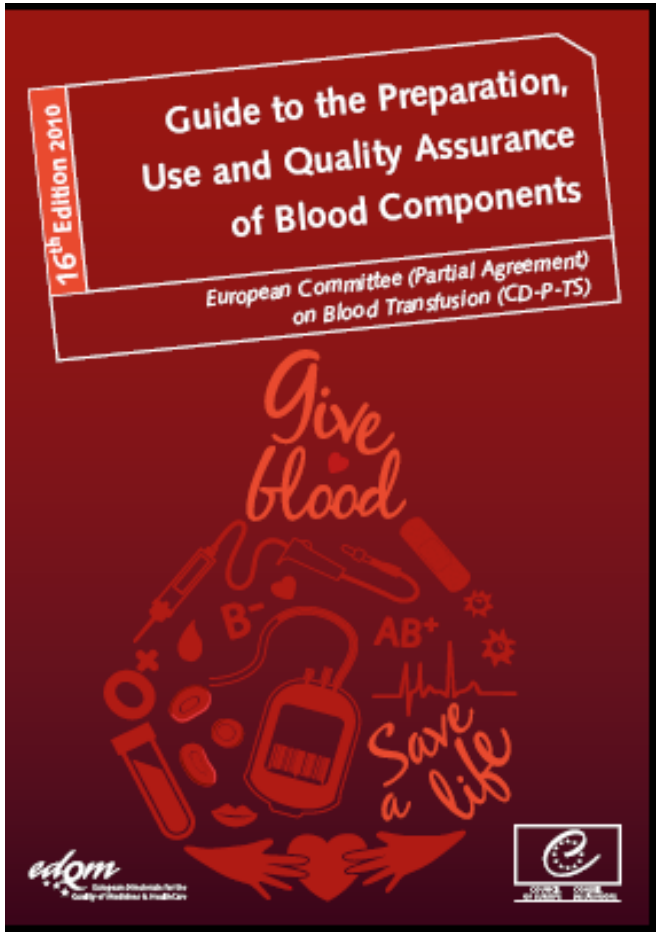
- The current strategies which include
- ➢ proper medical examination,
- ➢ screening of blood,
- ➢ filtration of blood to remove leucocytes,
- ➢ chemical inactivation of any infectious agent if present and
- ➢ haemovigilance system that help to identify emerging new TTI threats;
- ✓ by facilitating quality assurance,
- ✓ quality control and
- ✓ the ability to monitor all steps in the transfusion chain have produced a marked decrease in transfusion transmitted infection in recent years in India.
- The risk of infection by a contaminated blood unit today is comparatively lower than observed 30 years back.

Blood Transfusion -Guidance and Regulations

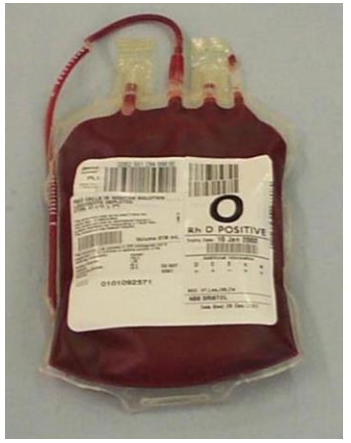
- **WHO recommendations**
- **safe and adequate blood supply**
- **also clinical transfusion process**
  - **Appropriate use of blood**
  - **Collection samples, patient ID**
  - **compatibility testing**
  - **Administration of blood**
  - **Adverse event reporting**
  - **Hospital transfusion committee**

- **‘Better Blood Transfusion’**
- **EU Optimal Blood Use manual**
- (www.optimalblooduse.eu)

- **Council of Europe**
- **47 member countries**



Safety of the Blood Supply



- Voluntary and non-remunerated donor
- Donor Health Questionnaire
- **Council of Europe - Mandatory screening tests**
  - **Hep B, Hep C, HIV 1 & 2**
  - **Additional testing – Syphilis, HTLV**
  - **Selective screening – Malaria, CMV**

Infective risks - UK

Infection	Testing started	Approximate risk of infection per unit of blood in UK
Hepatitis B	1975	1 in 1.06 million
HIV	1985	1 in 6 million
Hepatitis C (Anti HCV and NAT testing)	1991 &1998	1 in 72 million

Health Protection Agency

Management chronic viral hepatitis in thalassemia: recommendations of an international panel
Marco et al Blood **2010** 116 2875

Hep C antibody in thalassemia patients

Ref		no.	Anti-HCV⁺ %	
13 2006	Iran	732	19.3	
14 2006	Turkey	399	4.4	
15 2003	Thailand	104	21.2	
16 2002	Lebanon	395	14	
17 2001	India	104	21	
18	Malaysia	85	22.4	
21 2006	Iraq	559	67.3	
22	Pakistan	35	60	
23	Italy	1481	85.2	1998
24	Bahrain	242	20.5	
25	Brazil	32	46.8	
26	Hong Kong	99	34	
27	UK	73	23.3	

Wonke B et al Clin Pathol 1990;43:638

23.3% of 73 patients positive

Thompson et al **2011** Brit Journal of Haematol, 153, 121–128 Thalassemia Clinical Research Network Investigators:
169 of 697 Hep C Ab pos – 24%

Cunningham et al 2004 Blood 104, 34
5% patients aged<16yrs
23% aged 16-24yrs;
70% aged 25yrs or older

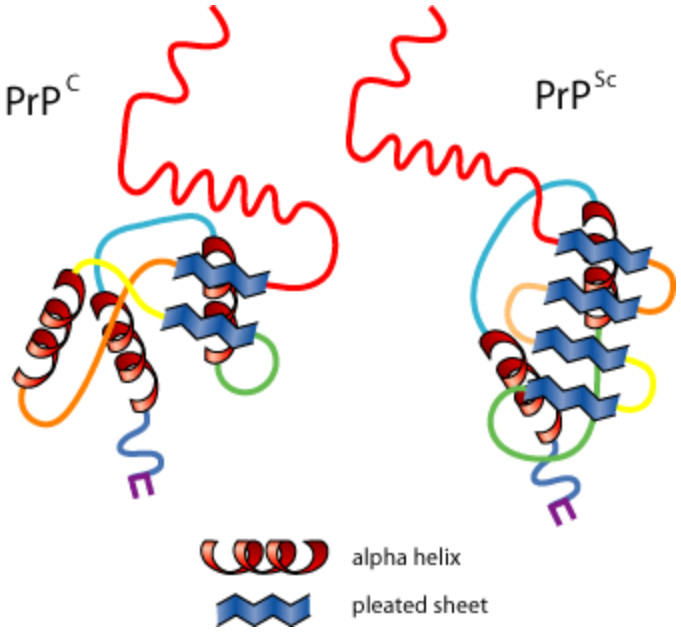
Variant CJD

- First noted in 1996
  - Distinct from sporadic CJD
  - Median age at presentation 26 years
  - Neuropsychiatric symptoms, ataxia, dementia.
  - Progression over 6 -40 months

  same strain of prion disease as Bovine Spongioform Encephalopathy (BSE)

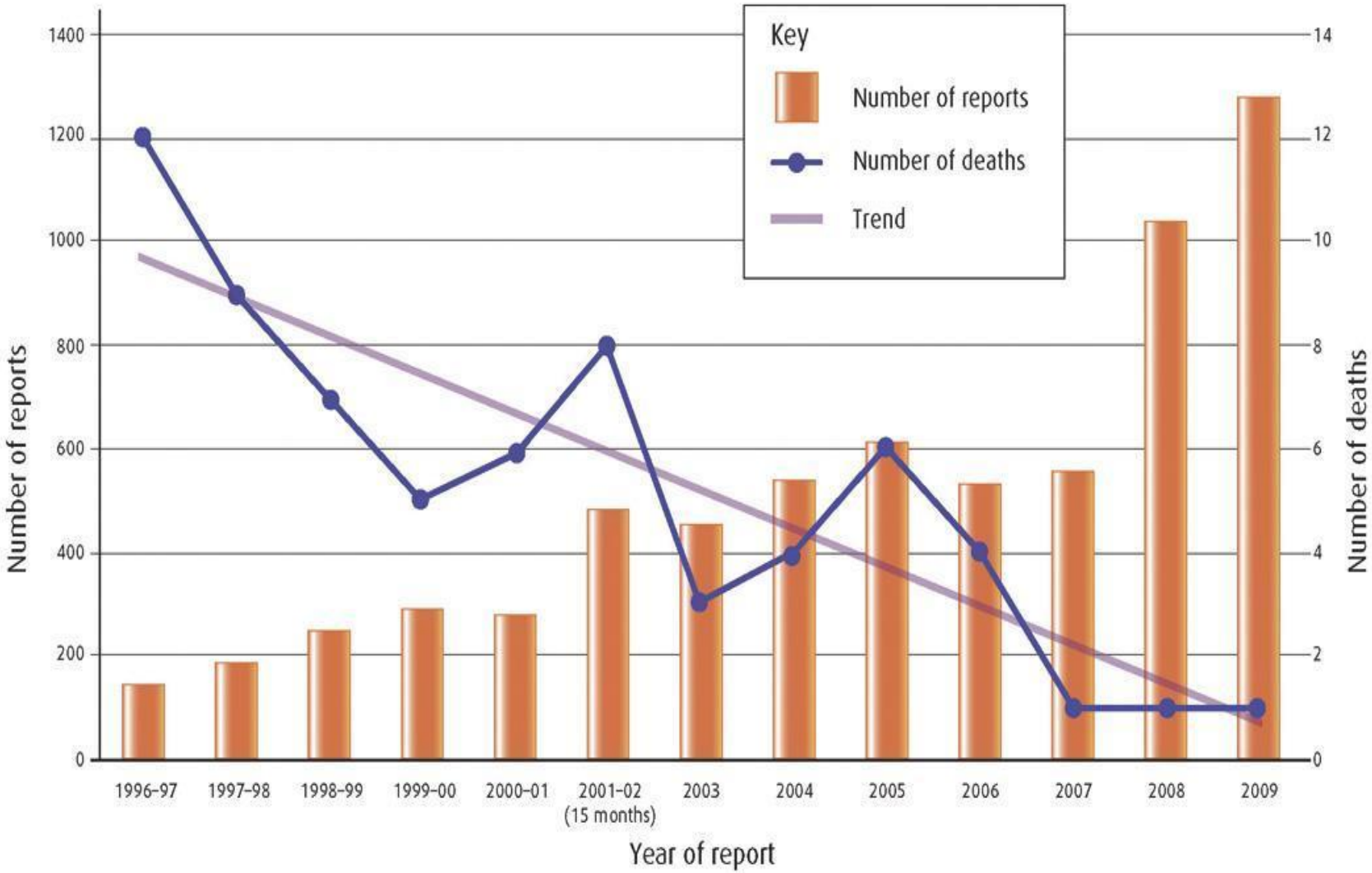
- 173 cases in UK

- 4 transfusion related cases
  - I case in Haemophilia patient



National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU)
www.cjd.ed.ac.uk

Trend in total reports and total deaths definitely due to transfusion



RESIDUAL INFECTIOUS DISEASE RISKS in TRANSFUSION

Disease Transmitted by Blood	Estimated Frequency per Unit
Hepatitis B virus	1 : 843,000 – 1,280,00
Hepatitis C virus	1 : 1,149,000
HIV- 1 / 2	1 : 1,470,00
HTLV – I / II	< 1 : ~ 3,000,000
WNV	<< 1 : ~ 4,000,000
Bacterial contamination (platelets)	1 : ~ 2000 – 3000 platelet transfusions

LOYOLA UNIVERSITY HEALTH SYSTEM

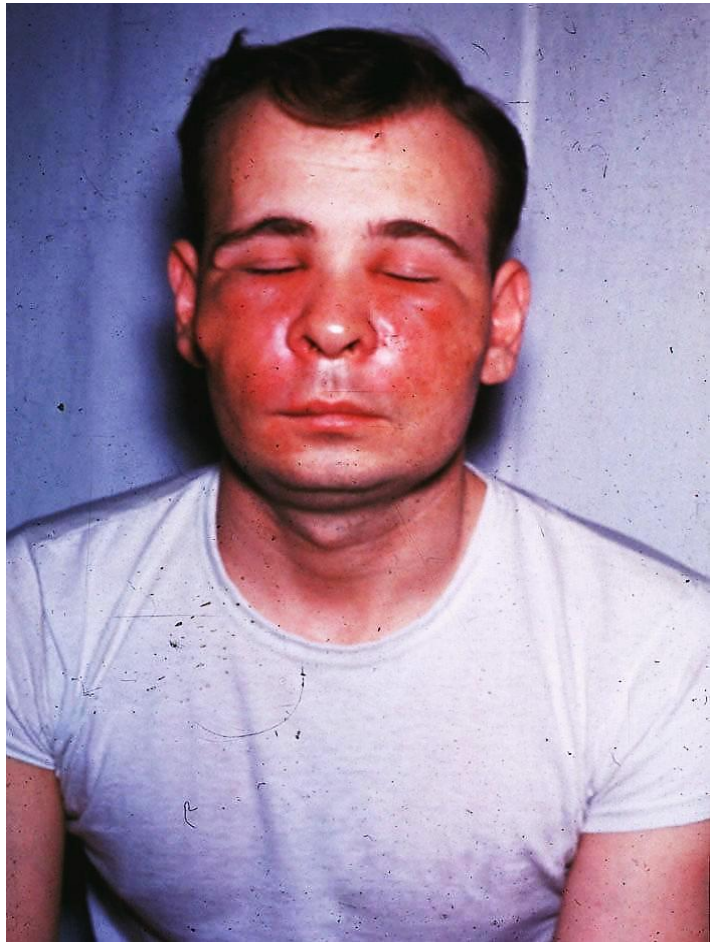
Next *Diseases of Concern* for Testing in the Blood Supply

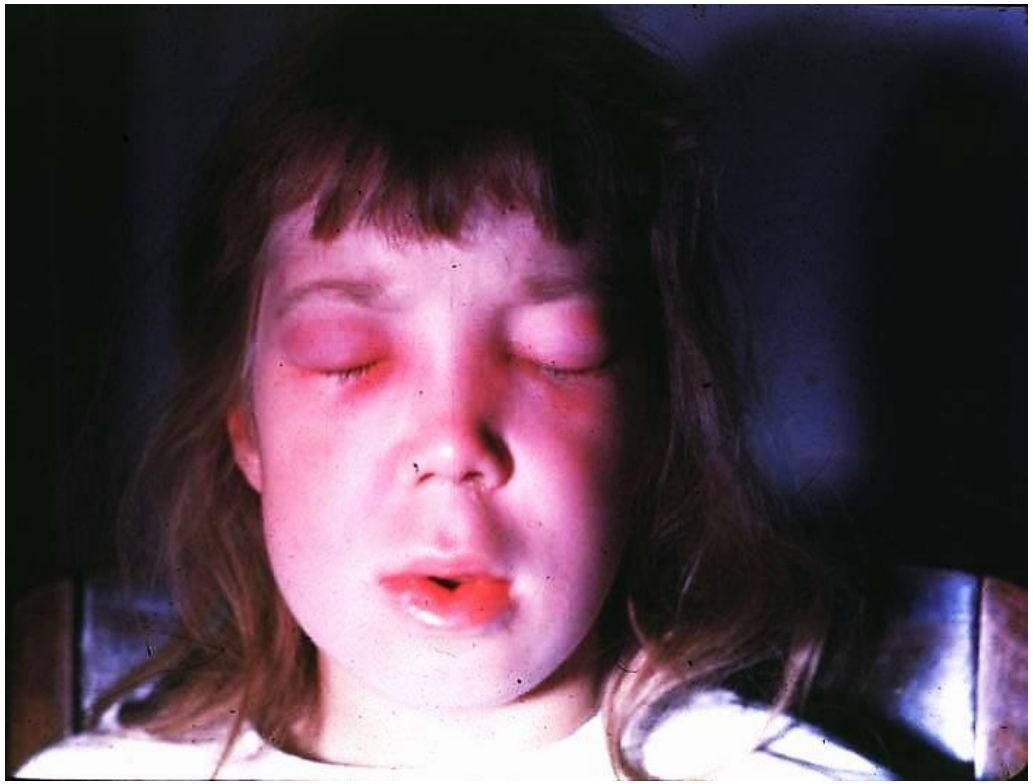
- Arboviruses
  - **Zika**, Dengue, Chikungunya
- *Babesia* species
- Parvovirus B19
- Human v-CJD

Emerging Infectious Diseases and their potential threat to transfusion safety, *Transfusion* 2009;49, 1S-29S.

LOYOLA UNIVERSITY HEALTH SYSTEM

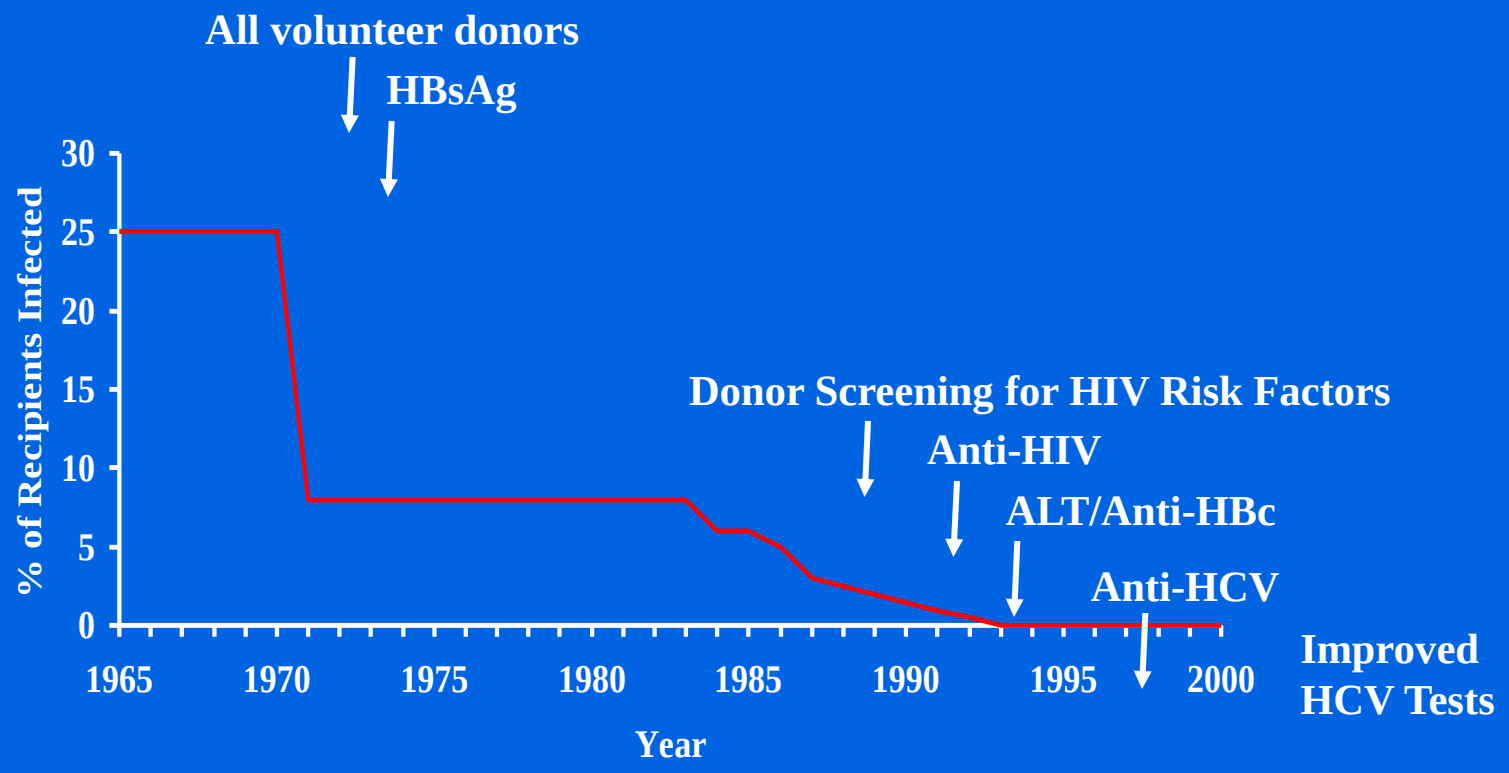
Allergic Transfusion Reactions: Hives and Itching



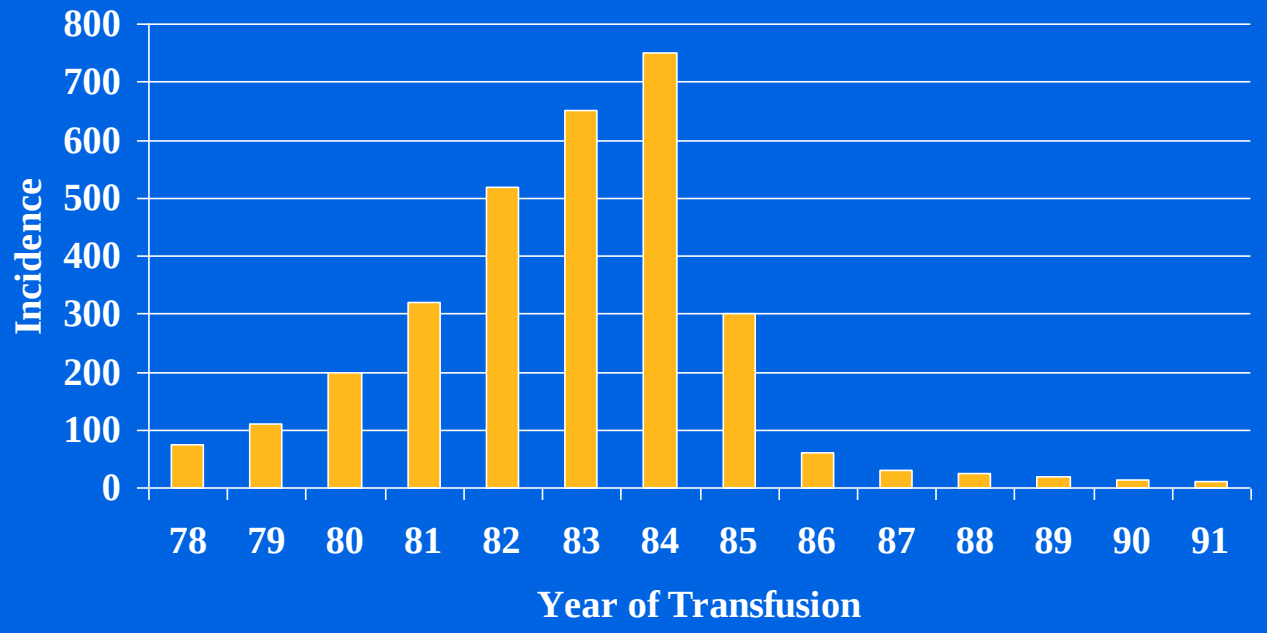


LOYOLA UNIVERSITY HEALTH SYSTEM

Posttransfusion Hepatitis C



Transfusion Transmitted HIV



Estimated Current Risks

- Hepatitis C
  - 1:1,800,000
- HIV
  - 1:2,300,000
- Hepatitis B
  - 1:1,500,000

West Nile Virus

- Latent period 3-15 days
- No chronic carrier state
- Blood donor prevalence: ~1:10,000
- Transfusion risk: <1:1,000,000

QUESTIONS?

Call the Biosafety Officer at 243-6395

Introduction

1981

2014

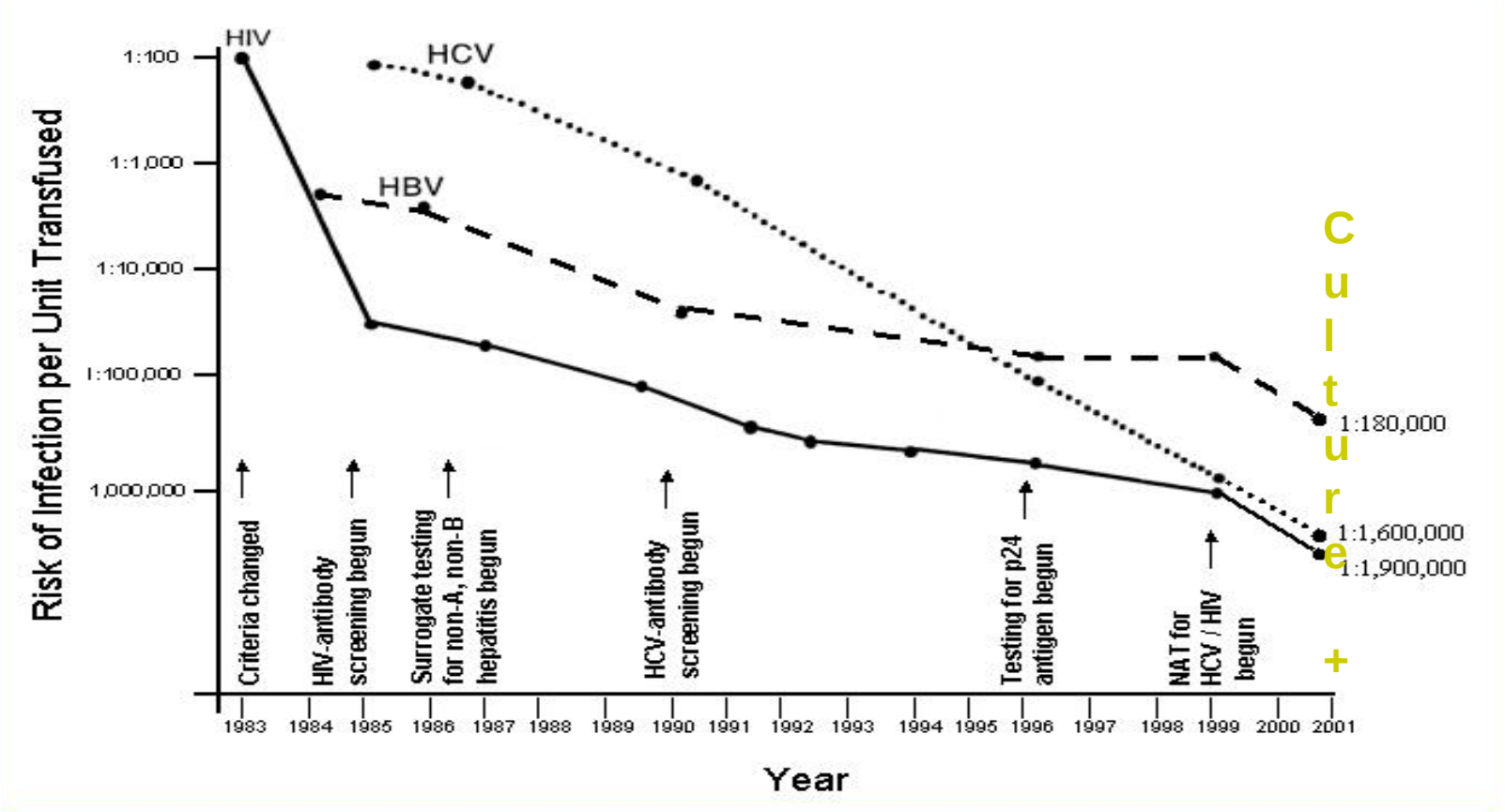
2016

- Over the years, there have been outbreaks of diseases around the world.
- Three examples of outbreaks that have affected the U.S.

1. include the 1981 outbreak of HIV,
2. the 2014 outbreak of Ebola, and, most recently,
3. the 2016 outbreak of the Zika virus.

- All three are examples of diseases that can spread through contact with infected blood or other bodily fluids.

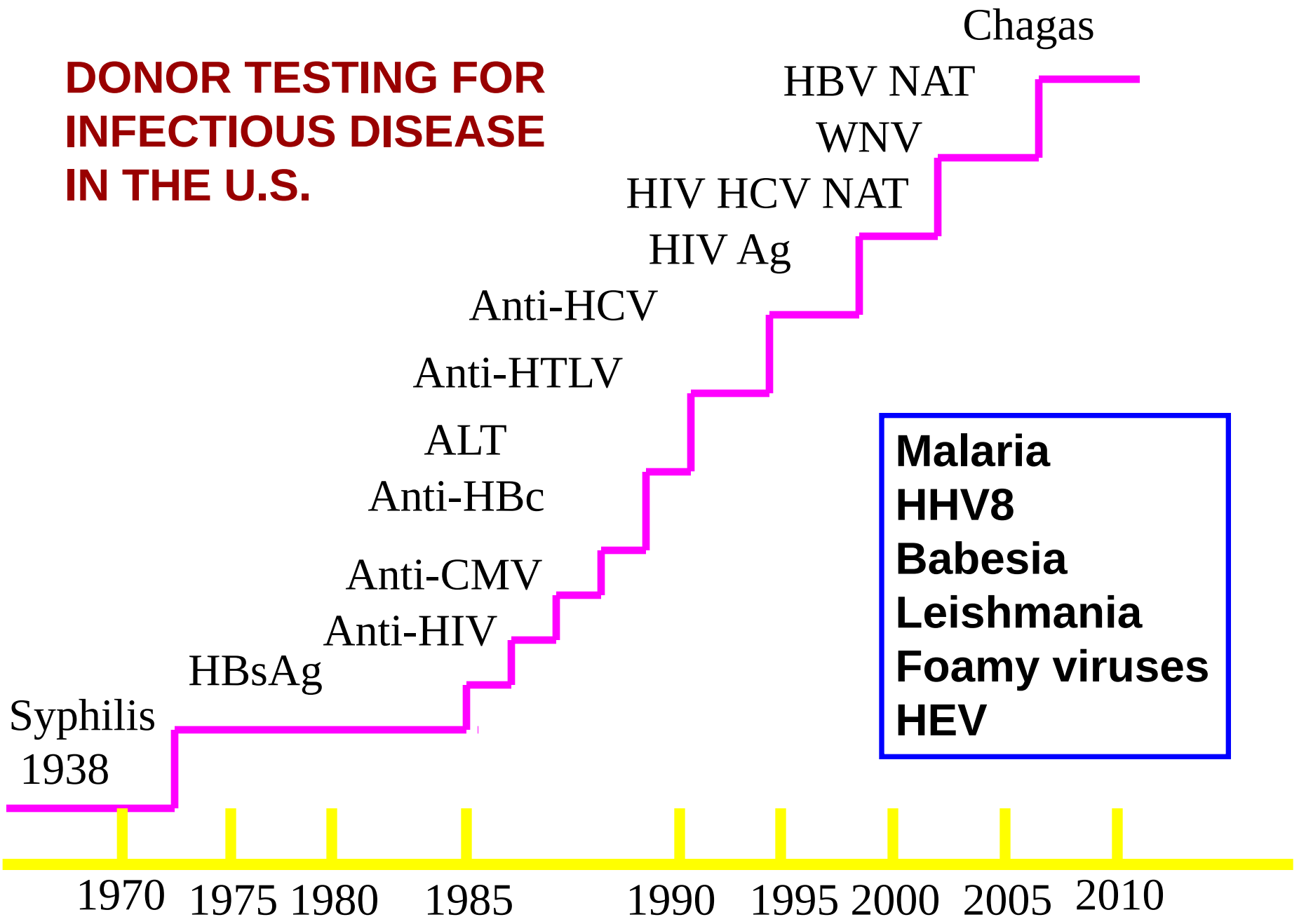
NEW TEST IMPLEMENTATION AND DECLINING RISK OF TA-VIRAL INFECTIONS IN THE U.S.



CURRENT DONOR TESTING FOR INFECTIOUS DISEASE

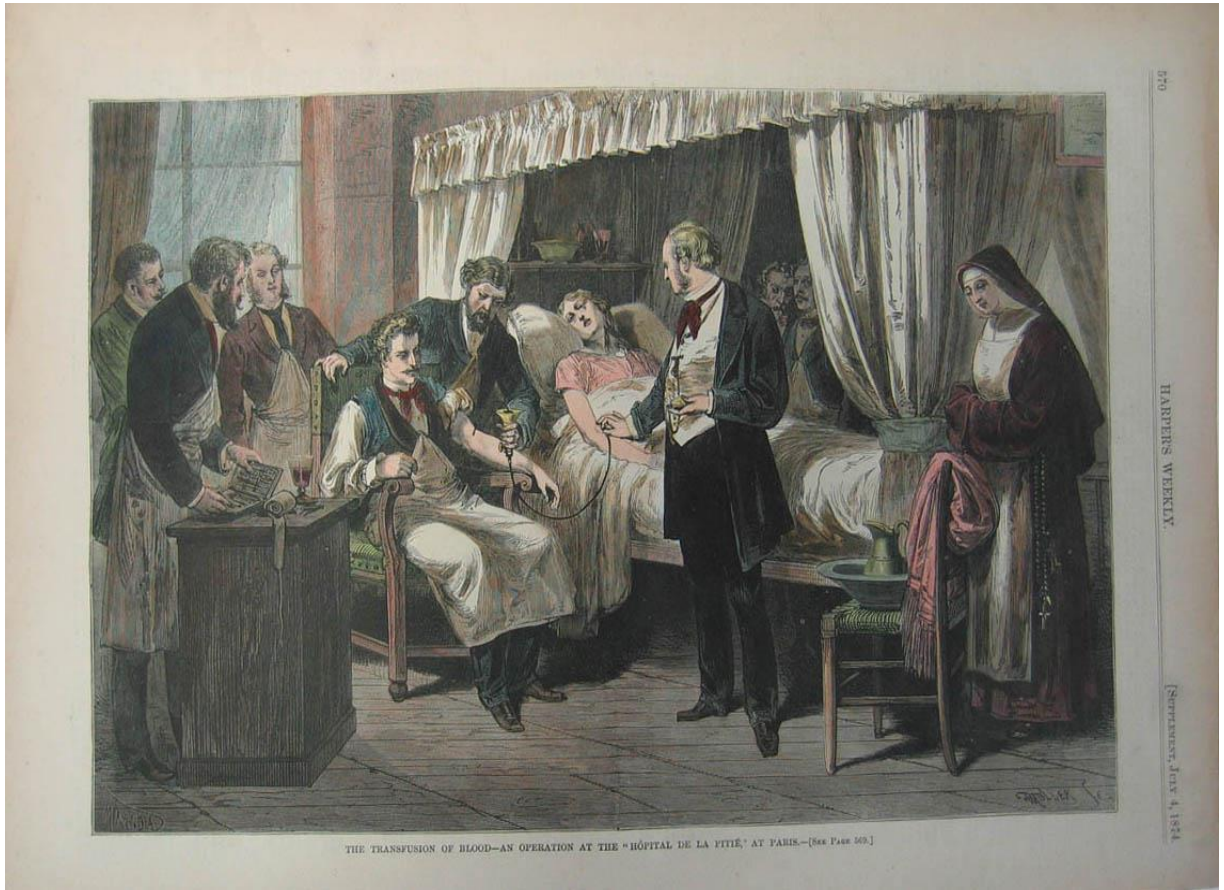
- Syphilis (1938)
- Anti-HIV
- Anti-HTLV
- HIV p24 Antigen
- WNV NAT
- Anti-HBc
- HB_sAg
- Anti-CMV
- Anti-HCV
- HIV and HCV NAT
- Bacteria (2004)
- Chagas Disease (2009)

DONOR TESTING FOR INFECTIOUS DISEASE IN THE U.S.



TRANSFUSION REACTIONS

- is any unfavorable transfusion-related event occurring in a patient during or after transfusion of blood components



Commission of Inquiry on the Blood System in Canada ('Tainted Blood Tragedy')

Justice Horace Krever, 1997

"The most influential report on public health in Canadian history"

-K. Wilson CMAJ 2007

The Tragedy

- **1,000 infected with HIV**
- **30,000 infected with hepatitis C**
  After being transfused blood between late 1970s and 1980s

- "Arguably the largest public heath catastrophe in the country's history"

-Picard, A. The Gift of Death 1995

The Canadian Red Cross

“Would it not be possible, in time of peace and quiet, to form relief societies for the purpose of having care given to the wounded in wartime by zealous, devoted, and thoroughly qualified volunteers?”

Henry Dunant, founder of the Red Cross in 1863

Transfusion Transmitted Infections

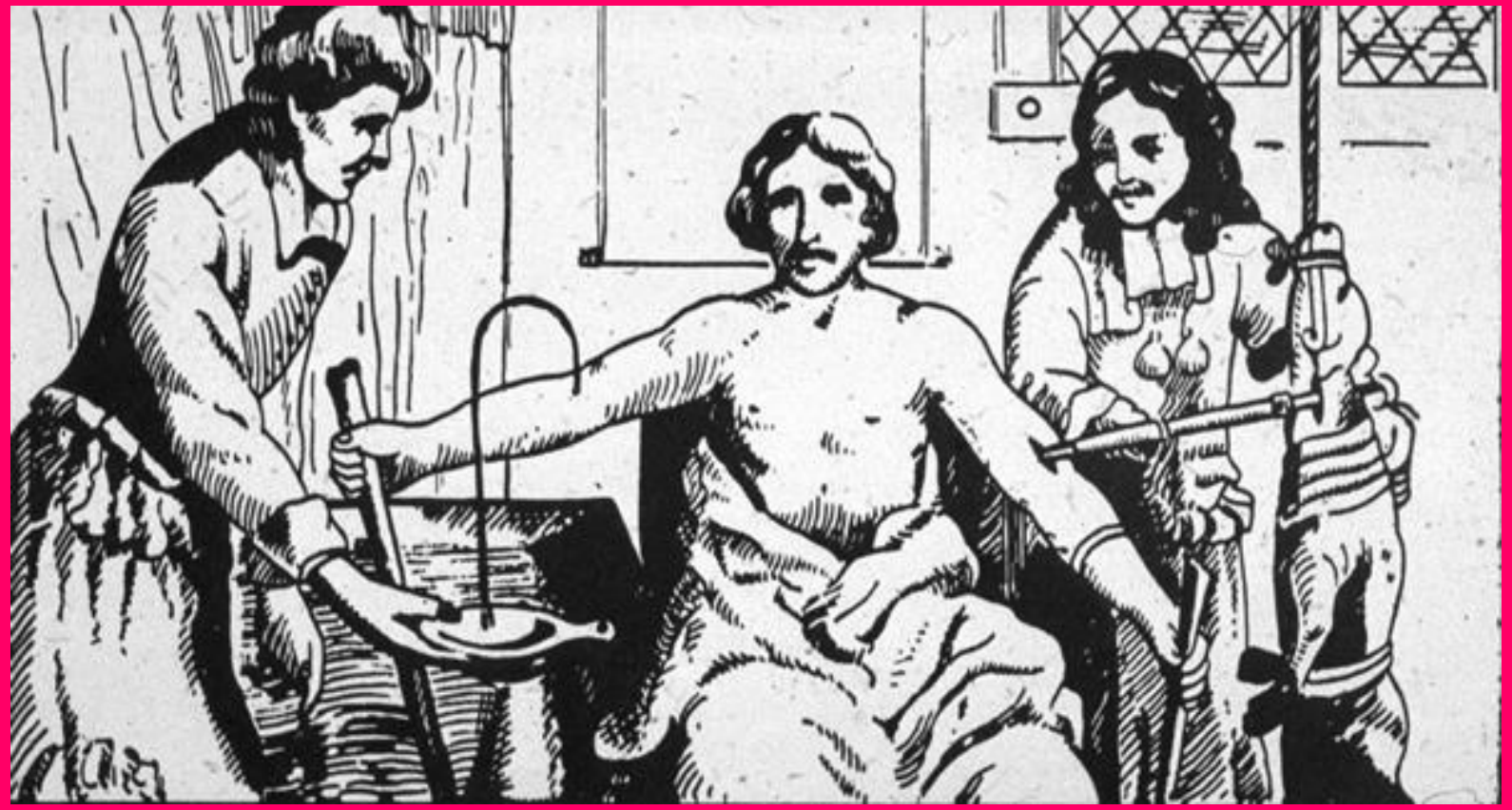
Dr. Feizollah Mansouri
Kermanshah Medical University
1394/7/11

TRANSFUSION

THE TRANSFUSION OF BLOOD—AN OPERATION AT THE "HÔPITAL DE LA FITIÉ," AT PARIS.—[See Page 569.]

570 HARPER'S WEEKLY. [SUPPLEMENT, JULY 4, 1874.

Animal to Human Transfusion



Early lamb blood transfusion

Jean Baptiste Denis

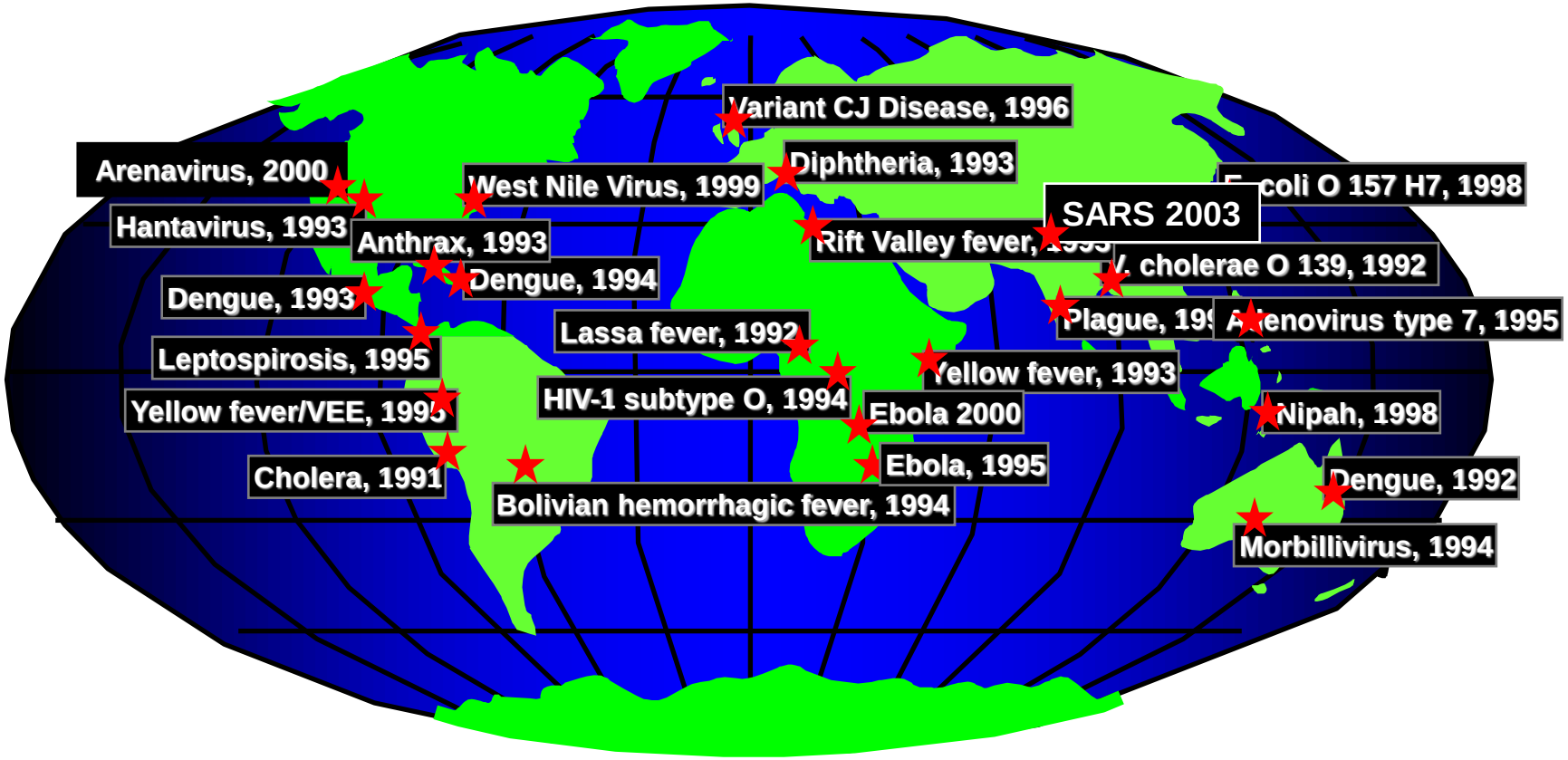
- Denis and Emmerez performed transfusion of lamb blood into the carotid artery of a young woman in 1667.
- Denis reported that the woman passed urine as black as soot following the transfusion, a finding indicative of a hemolytic transfusion reaction, but she survived.

Transfusion Transmitted Infections

- Blood transfusions ***saves countless numbers of lives***, but they can also transfer **a number of different infections.**
- Although the risk of transfusion-transmitted infections today is **lower than ever**,
  - ***the supply of safe blood products*** remain subject to contamination with *known* and
  - yet *to be identified human pathogens.*

New and (Re)Emerging Agents Not Tested

(1991-2003)



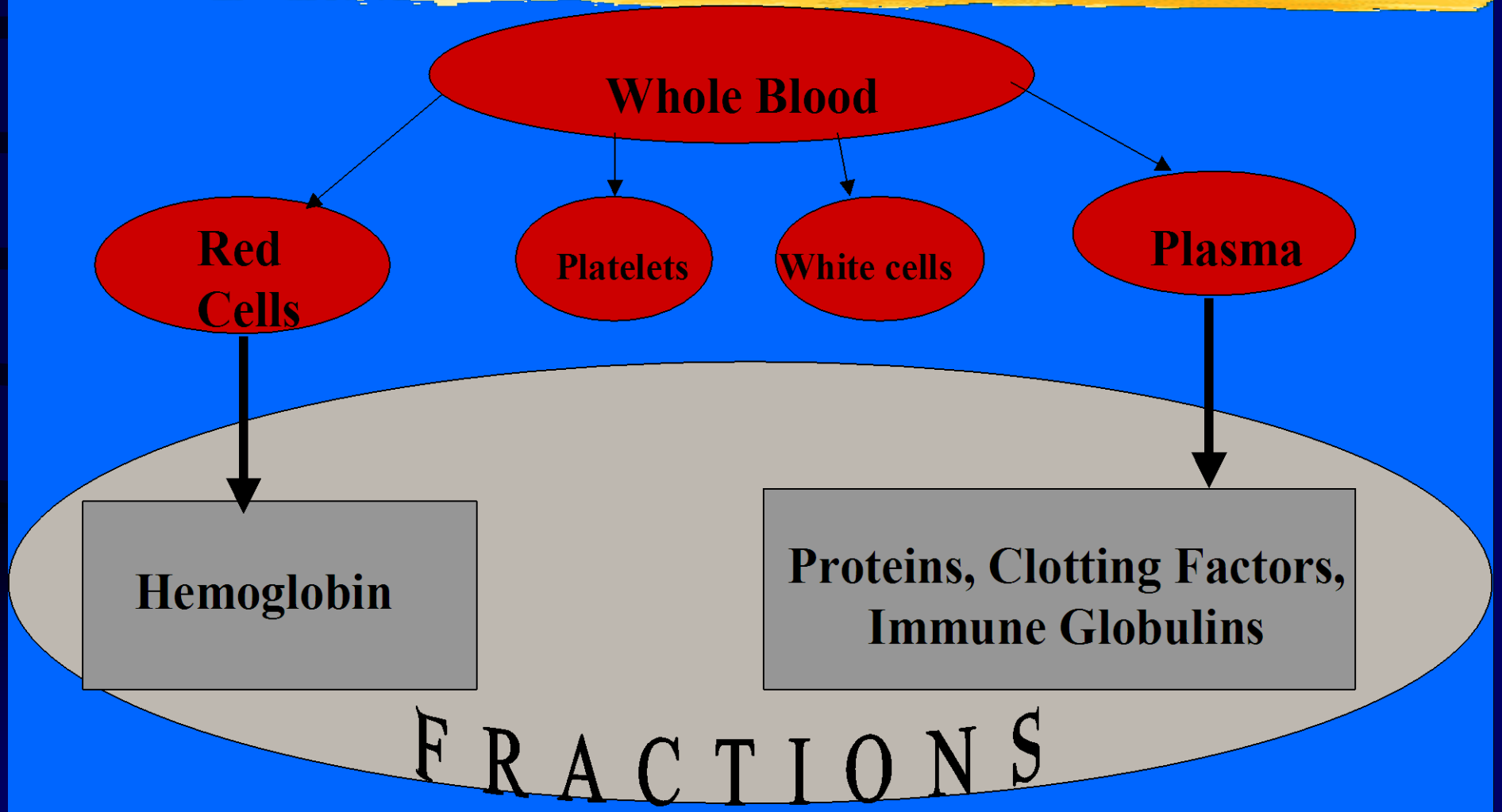
kindly provided by Dr. B Horowitz

Transfusion – Associated Infections

- As we manage to control the known threats, however,

  new challenges will continue to arrive.

Blood - Its Components



Transfusion – Associated Infections

- Beeson reported the first cases of transfusion-associated infection in 1943, describing **seven patients**, who developed **hepatitis** from 1 to 4 months after receiving a red blood cell (RBC) or plasma transfusion.

Laboratory Support Challenges for Blood Transfusion Safety

Relevance of Blood Transfusion Safety Activities

- Approximately 90 million transfusions worldwide annually
- 31% of transfusions not screened for HIV, Hepatitis B or Hepatitis C
- Most laboratory screening lapses occur in developing countries

Source: WHO, GDBS 2001

Relevance of Blood Transfusion Safety Activities

Annually, unsafe blood transfusions are estimated to be responsible for

- 10,000 new HIV infections
- 78,000 new HBV infections
- 500,000 new HCV infections

Transfusion Transmitted Infections

- The infections transmitted through blood can be divided into:

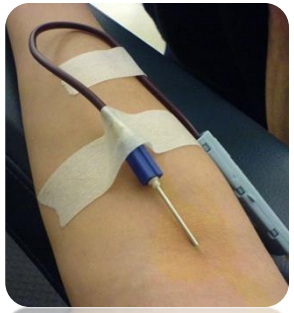
1. **Exogenous**
2. **Endogenous**

- The infectious agents known to be transmitted through blood can be

- Viruses
  - cell-associated
  - plasma associated
- Bacteria
- protozoa

Sources of contamination

- Donor bacteremia



- Phlebotomy core
- Skin surface contaminants

- Containers and disposables
- Environment

Transfusion Transmitted Infections

- **Endogenous microbiological** agents transmitted by blood transfusion have certain characteristics and the hallmark is persistence of infection i.e.
  - Long incubation period
  - Carrier or latent state
  - Ability to cause asymptomatic/subclinical infection
  - Viability and stability in stored blood or plasma

Transfusion Transmitted Infections

- Viruses transmissible by blood transfusion

  <u>Cell associated viruses</u>

  - CMV
  - EBV
  - HTLV1 and HTLV II
  - HSV-1 and HSV2

Transfusion Transmitted Infections

- ***Plasma associated viruses***
  - Hepatitis B virus (HBV)
  - Hepatitis Delta virus (HDV)
  - None-A non-B hepatitis/(one of which is Hepatitis C virus) HCV
  - HIV-1 & HIV-2
  - Human parvovirus (B19)

Transfusion Transmitted Infections

- Bacteria and parasite transmissible by blood transfusion

Bacteria

- Treponema pallidum (syphilis)
- Brucella abortus
- Yersinia enterocolitica
- salmonella

Transfusion Transmitted Infections

Parasites

- Plasmodium species (malaria)
- Trypanosoma cruzi (Chagas disease)
- Toxoplasma gondii (mostly immunosuppresed patients)
- Leishmania donovani
- Microfilaria
- Babesia microti

Transfusion Transmitted Infections

Bacterial contamination

- The risk of bacterial infection has emerged as the major cause of transfusion related morbidity and mortality, in part due to reduction of other risk.
- Bacterial contamination is more frequent in
- ✓ ***platelets concentrates (PLT)*** than in
- ✓ **red blood components** most likely because many microorganisms can survive and propagate under storage conditions typically used for **PLT (20-24˚C)** but less so for ***RBC*** **(1-6˚C)**.

Transfusion Risks

Bacterial Contamination:

Platelets	1:2,500
Red Blood Cells	< 1:1,000,000

Transfusion Transmitted Infections

Bacterial contamination

- The bacteria implicated in bacterial reactions associated with **RBC** are typically gram-negative bacilli such as
  - ***Yersinia enterocolitica*** and ***Pseudomonas fluorescence***.

- In contrast, bacteria implicated in reactions associated with **platelets** are mostly gram-positive species such as
  - ***Staphylococcus*** and ***Streptococcus species***.

Microbiologic spectrum of transfusion-transmitted bacterial contamination

- A multitude of microorganisms have been isolated from contaminated blood products.
- Some of these organisms and species include the following:

✓ *Yersinia*,

✓ *Proteus*,

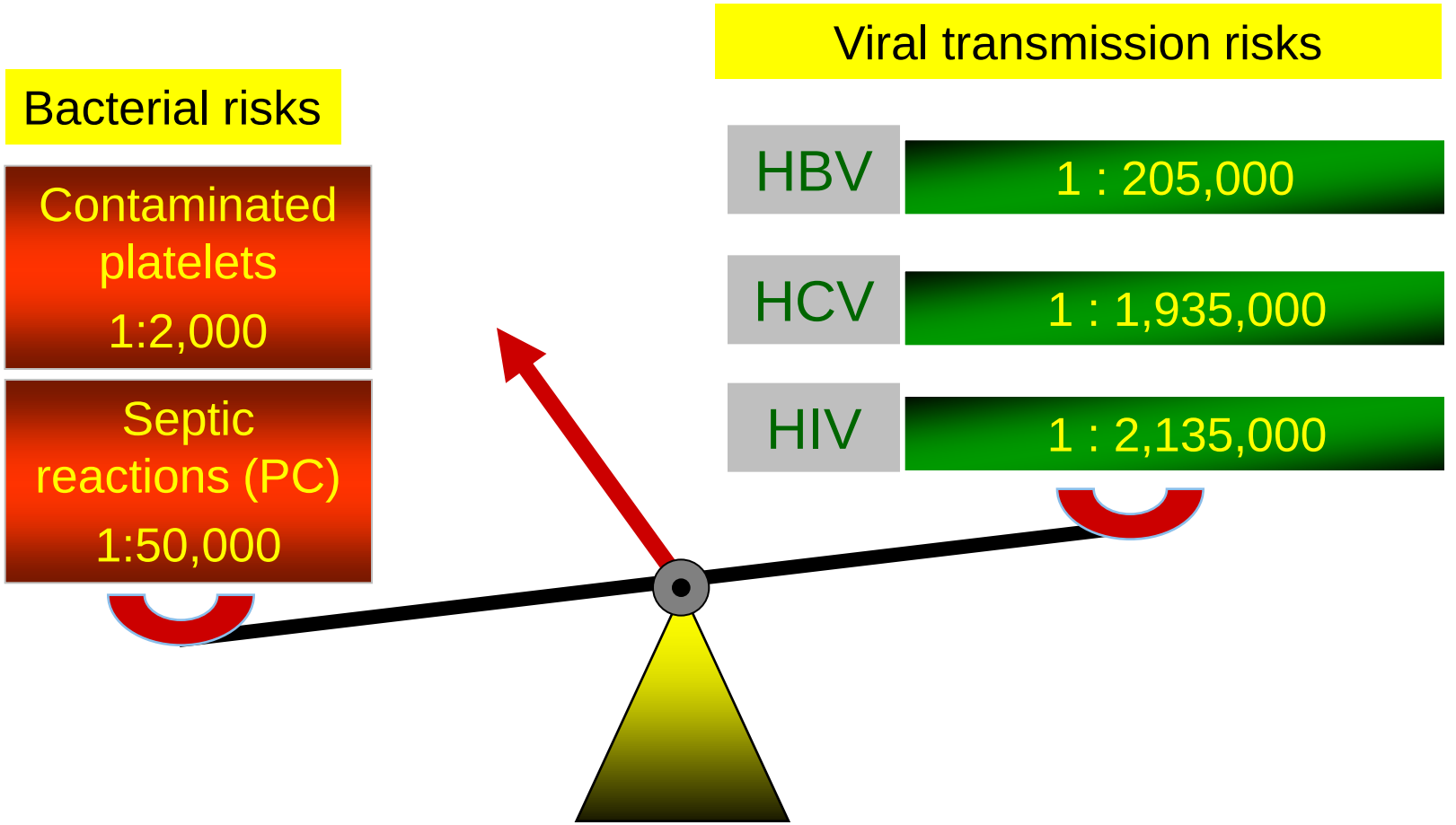
✓ *Pseudomonas*,

✓ *Escherichia*,

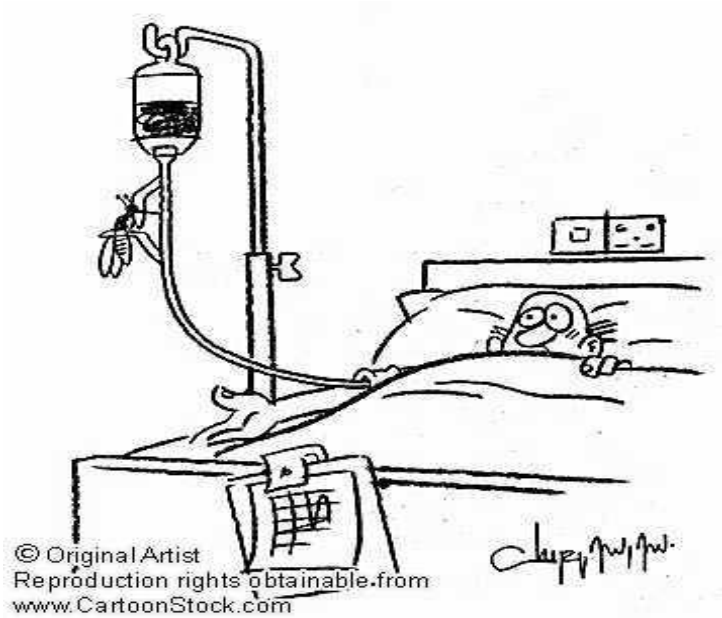
✓ *Klebsiella*, *Acinetobacter*, and*Serratia*, while among gram-positive organisms,

✓*Propionibacterium*,*Staphylococcus*, *Bacillus,* and *Enterococcus* were isolated

Residual Bacterial Risk Remained



Infectious Risks of Transfusion



Bloodborne Pathogens

Transfusion Transmitted Injuries Section
Transfusion Transmitted Diseases/Infections

25 Reported TTIs

- Human Immunodeficiency Virus
- Human T-Lymphotropic Viruses type I and type II
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis E
- Hepatitis G virus/GB virus C
- Cytomegalovirus
- Epstein-Barr Virus
- Human Parvovirus B19
- Human Herpesvirus 6
- Human Herpesvirus 8
- TT Virus
- SEN Virus
- CJD and vCJD
- Bacterial Contamination
- Syphilis
- Malaria
- Chagas' Disease
- Toxoplasmosis
- Leishmaniasis
- Lyme disease
- Babesiosis
- Rocky Mountain Spotted Fever
- Ehrlichiosis

TABLE 306-1 List of Notable Infections Transmitted by Blood Transfusion
Viruses
Cytomegalovirus
Colorado tick fever virus
Dengue virus
Epstein-Barr virus
Hepatitis A virus
Hepatitis B virus
Hepatitis C virus
Hepatitis E virus
Human herpesvirus 8
Human immunodeficiency virus 1 and 2
Human T-lymphotropic virus 1 and 2
Parvovirus B19
Tickborne encephalitis virus
West Nile virus
Bacteria
Anaplasma phagocytophilum
Brucella spp.
Coxiella burnetii
Ehrlichia
Gram-positive organisms*
Gram-negative organisms†
Rickettsia rickettsii
Treponema pallidum‡
Parasites
Babesia spp.
Leishmania spp.
Trypanosoma cruzi
Plasmodium spp.
Prions
Variant Creutzfeldt-Jakob disease

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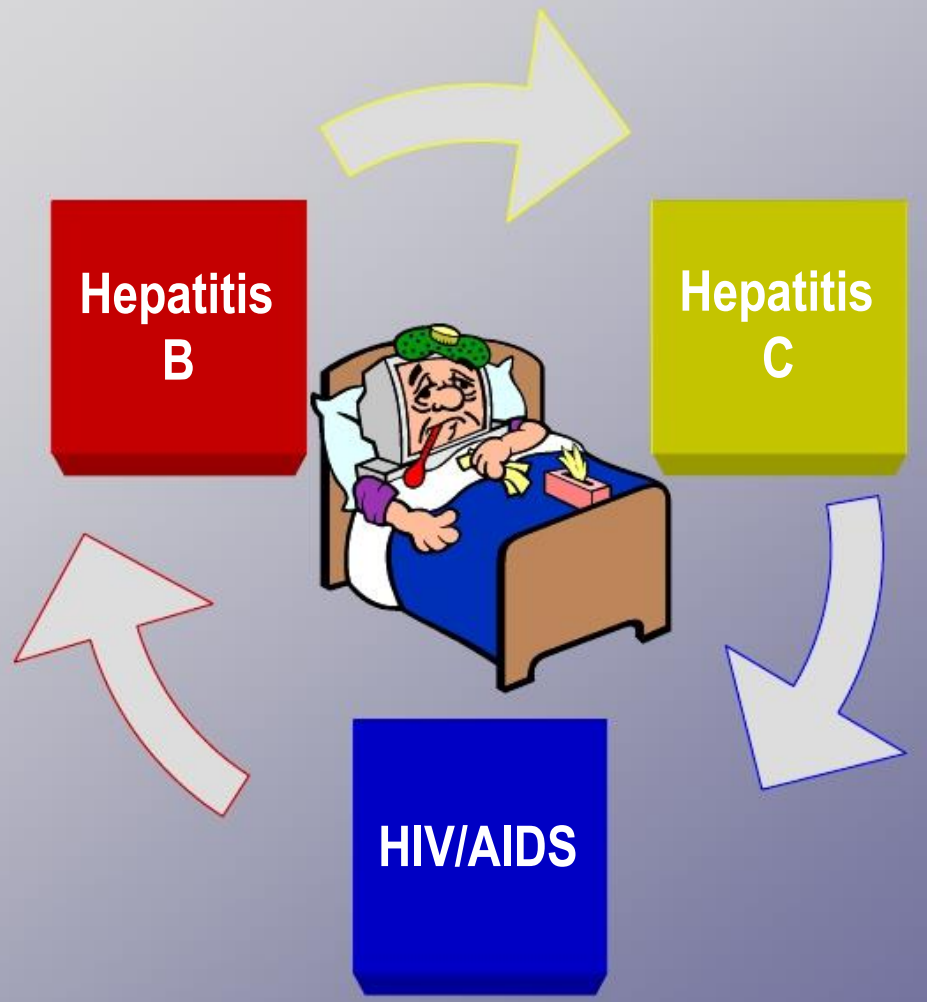
Variant Creutzfeldt-Jakob disease

The Big Three



Transfusion Risks

Infections:

The known risks of transfusion-transmitted diseases are estimated as follows:

HIV (type I)	**1:1,800,000**
Hepatitis C	**1:600,000**
Hepatitis B	**1:220,000**

overview

- Blood transfusion has been and continues to be a possible source of disease transmission.
- A myriad of agents can potentially be transmitted through blood transfusions, including
  - bacteria,
  - viruses, and
  - parasites.
- Of these, bacteria are the most commonly transmitted.

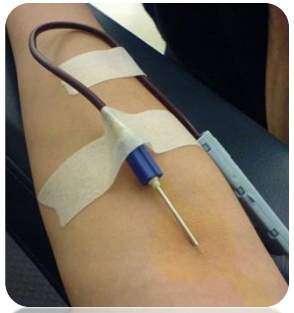
- Viral agents that are capable of being transmitted through blood transfusion include the following:
- Human immunodeficiency virus (HIV)
- Hepatitis viruses
- West Nile virus (WNV)
- Cytomegalovirus (CMV)
- Human T-cell lymphotrophic viruses (HTLVs)

Bacterial Infections

- Bacteria or, for that matter, any infective agent that potentially evades the sterility of the transfusion loop can come from the
  - donor's blood or skin or
  - from a contaminated environment.
- As previously stated, however, bacteria are most common infective agents to be transmitted through blood transfusion

Sources of contamination

- Donor bacteremia
- Phlebotomy core



- Skin surface contaminants
- Containers and disposables

- Environment

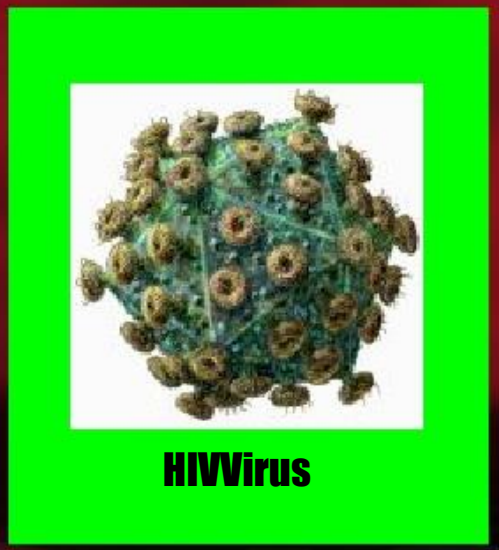
Human Immunodeficiency Virus (HIV)

HIV is the virus that leads to AIDS

HIV depletes the immune system

HIV does not survive well outside the body

There is still no vaccine available



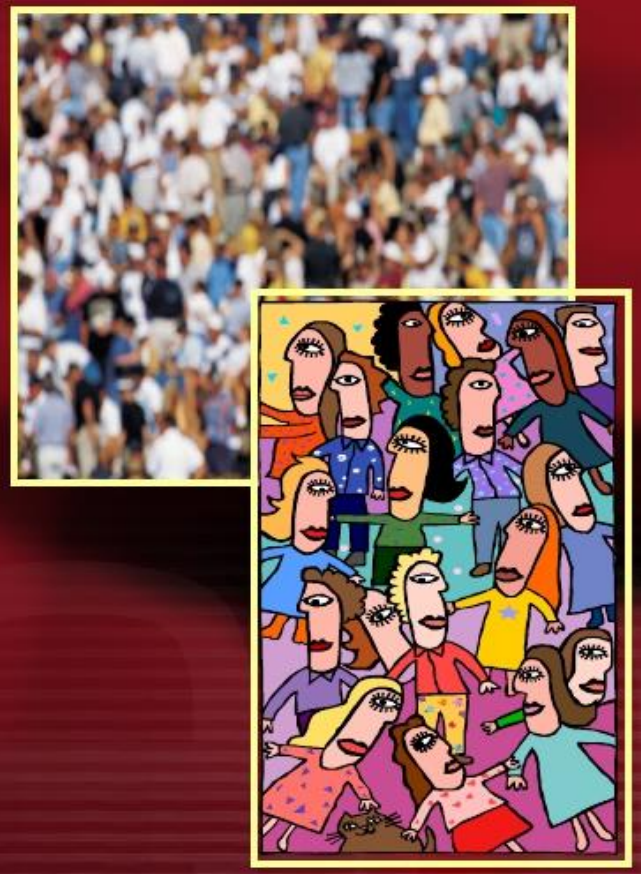
Some alarming facts of the HIV/AIDS tragedy in the USA

1 million people in USA have HIV/AIDS

Approximately 11 of every 1,000 adults (ages 15 to 49) are HIV infected

24-27% undiagnosed and unaware of their HIV infection

Women are the fastest growing group to be infected with HIV



Transfusion Transmitted Infections

Human Immunodeficiency Virus (HIV)

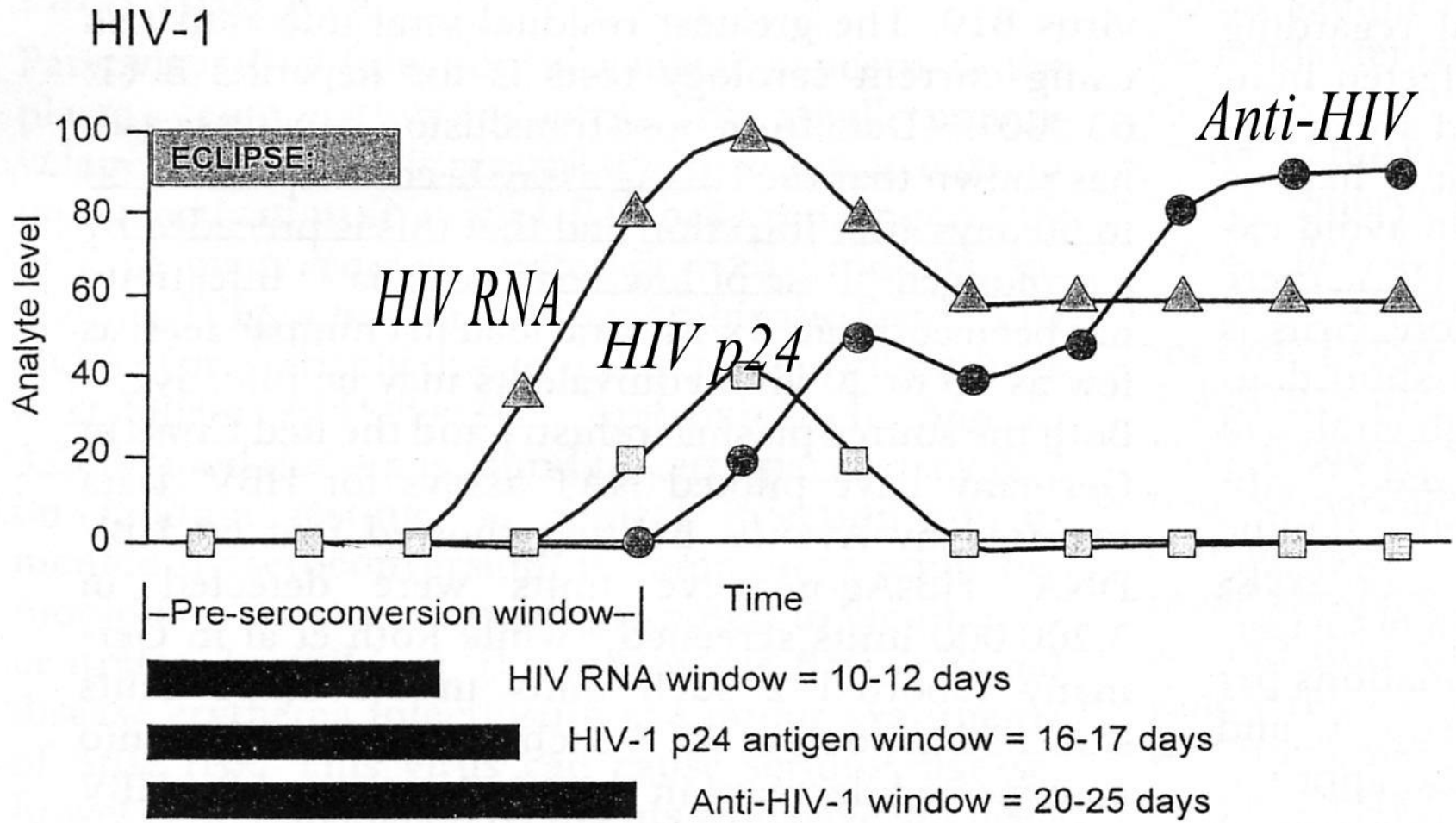
- The risk of HIV transmission through blood transfusion was estimated to be **1 in 752,000** donation between **1987 and 1996**.

- The risk has been estimated to be **1 in 1.3 million donation** following the implementation of **HIV-1 p24 testing**, and **1 in 1.6 million donations** following the implementation of **HIV NAT on pool of 24 samples**.

Transfusion Transmitted Infections

Human Immunodeficiency Virus (HIV)

- Laboratory technologies such as HIV-1 p24 antigen test and *HIV nucleic acid amplification testing (HIV NAT)* have significantly reduced the window period, **from 42 days by HIV antibody assays** in the 1980s **to 16 days by HIV-p24 antigen test** and **13 days by HIV NAT**.


HIV-1
Anti-HIV
ECLIPSE
HIV RNA
HIV p24
100
80
60
40
20
0
Analyte level
Time
–Pre-seroconversion window–
HIV RNA window = 10-12 days
HIV-1 p24 antigen window = 16-17 days
Anti-HIV-1 window = 20-25 days

Risk of Infection from Allogeneic Blood Transfusion

Virus	Risk
Hepatitis C	<1:1,000,000
Hepatitis B	1:140,000
HTLV I & II	1:640,000
HIV	<1:2,000,000

Infectious Risks of Blood Transfusion, *Blood Bulletin*, volume 4, No. 2, December 2001.

HIV

- The three major routes of transmission are unprotected sexual intercourse, contaminated needles, and transmission from an infected mother to her baby at birth, or through breast milk.
- Screening of blood products for HIV in the developed world has largely eliminated transmission through blood transfusions or infected blood products in these countries.

Viral Infections

- **Human immunodeficiency virus**
- The human immunodeficiency virus (HIV), a member of the Lentivirus family of retroviruses, is the causative agent of acquired immunodeficiency syndrome (AIDS).
- The estimated number of HIV-infected people in the United States ranges from 850,000 to 950,000.[17]
- Individuals who engage in male-male sexual behavior are the largest group of patients at risk;[18]

  less than 1% of HIV cases are attributed to blood or blood product transfusions.

Viral Infections

- **Human immunodeficiency virus**
- **Note:** The risk of transmission of HIV through blood products is as follows
- United States - 1 in 2 million units (2,135,000)
- Canada - 1 in 7.8-10 million units in Canada
- Parts of Europe - 1 in 1 million to 1 in 5 million units

Viral Infections

- With the 2002-2003 licensure of HIV minipool nucleic acid testing (MP-NAT), HIV-1 p24 antigen testing has been eliminated as a blood donor screening test.
- This is because the window period reduction that is achieved with the antigen test is only 6 days, compared with a window period reduction of approximately 11 days with NAT.

Viral Infections

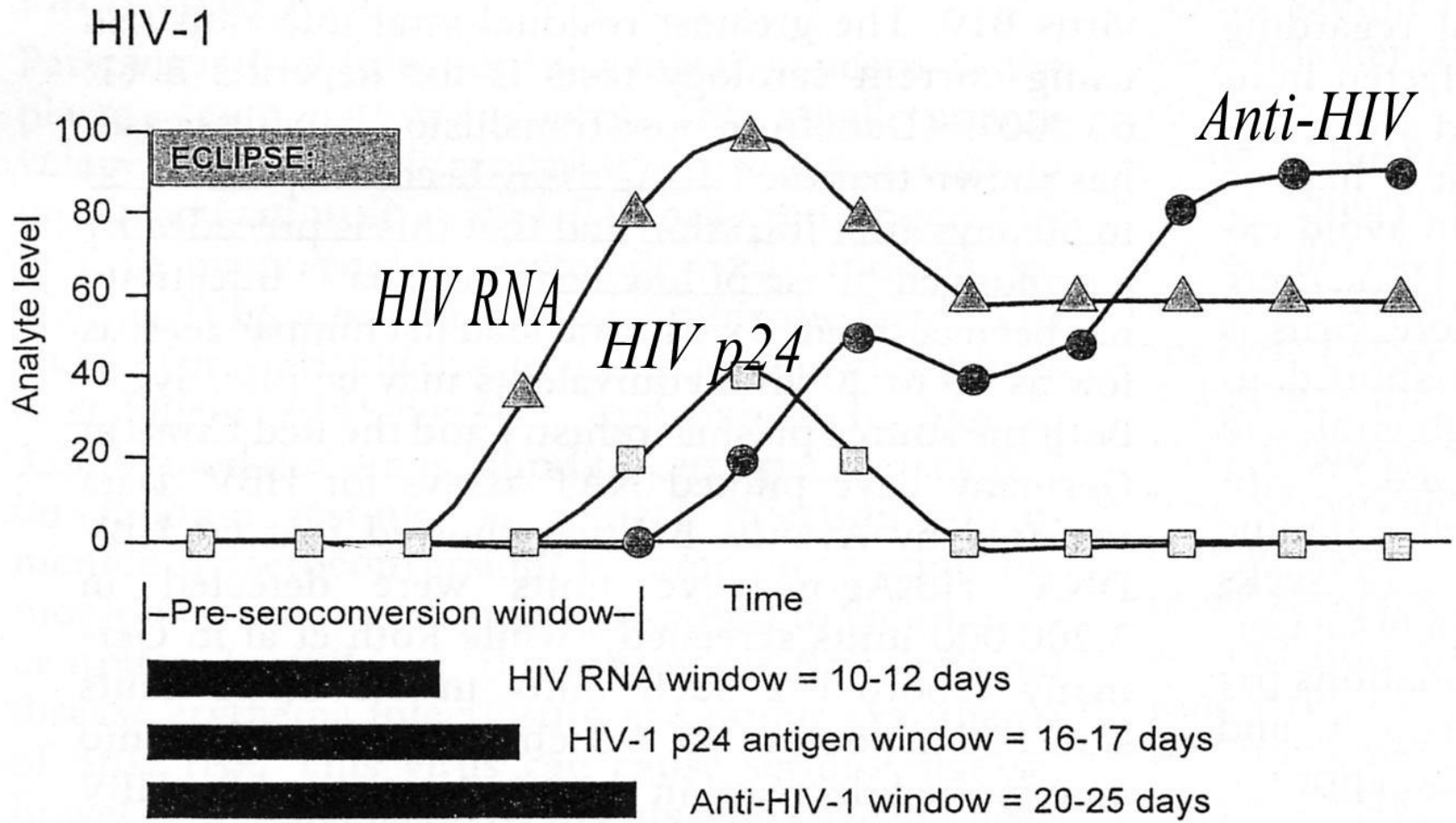
- MP-NAT detects viral ribonucleic acid (RNA) rather than the p24 protein;

✓ because the viral RNA appears in blood before p24,

an infection can be detected earlier,

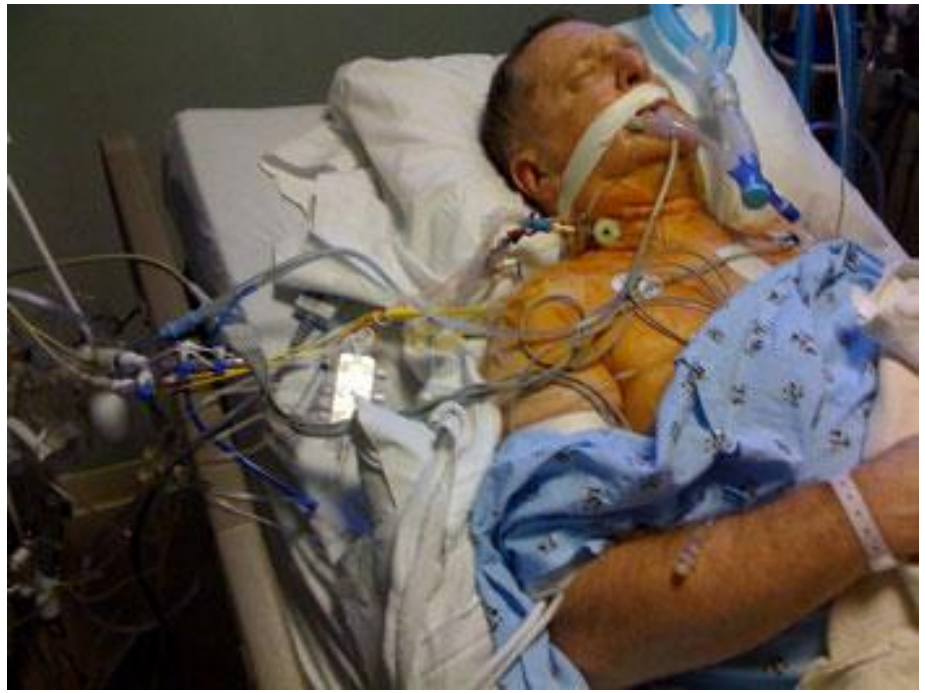
and the window period is therefore reduced.

- Furthermore, all p24-antigen–positive, anti-HIV–negative donors are positive in HIV MP-NAT.[22, 23, 24]
- HIV-positive individuals are permanently deferred from blood donations.


HIV-1
Anti-HIV
ECLIPSE
HIV RNA
HIV p24
100
80
60
40
20
0
Analyte level
Time
–Pre-seroconversion window–
HIV RNA window = 10-12 days
HIV-1 p24 antigen window = 16-17 days
Anti-HIV-1 window = 20-25 days

Good quality costs

Poor quality costs more



HIV-1 Minipool NAT Failures

Hepatitis B, hepatitis C and HIV transfusion-transmitted infections in the 21st century

D. M. Dwyre, L. P. Fernando & P. V. Holland
Department of Pathology, University of California Davis Medical Center, Sacramento, CA, USA

Dwyre et al, Vox Sang 2011

VoxSanguinis

REVIEW

Five cases of HIV transmission by donations negative by NAT minipool testing have been reported in the United States from four donors [32, 33], one in Germany [5] and one in France [34]. In working up these transmissions in detail, there are several common findings: The viral load was too low to be detected by pooled testing which generally requires > 90 copies/ml. By look back, it was determined that these donors' seroconversions were recent, thus explaining the low viral load. More important, further questioning of the involved donors revealed risk factors, specifically recent male to male sexual contact, that were denied in the original screening interview. Retesting of stored donor samples with ID NAT was reactive in the cases where it was performed.

the virus. Similarly, HIV minipool NAT–negative units have transmitted HIV, as recently as 2007; likely, these transmissions would have been prevented with single-unit NAT testing. Newer technologies, such as pathogen inactivation (PI), will

Failure of Routine HIV-1 Tests in a Case Involving Transmission With Preseroconversion Blood Components During the Infectious Window Period

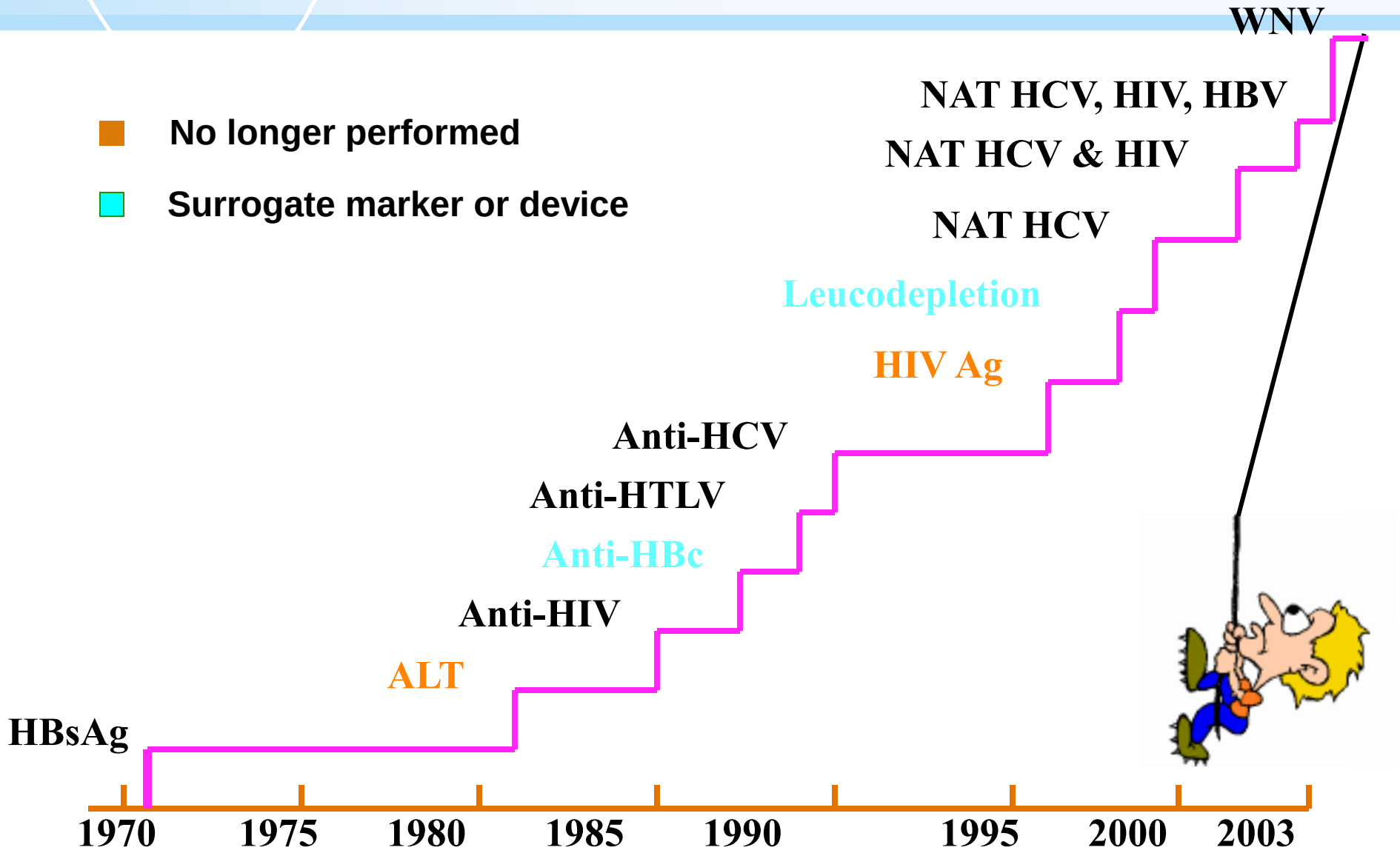
Al Ee Ling; Kenneth E. Robbins; Teresa M. Brown; et al.

JAMA. 2000;284(2):210-214 (doi:10.1001/jama.284.2.210)

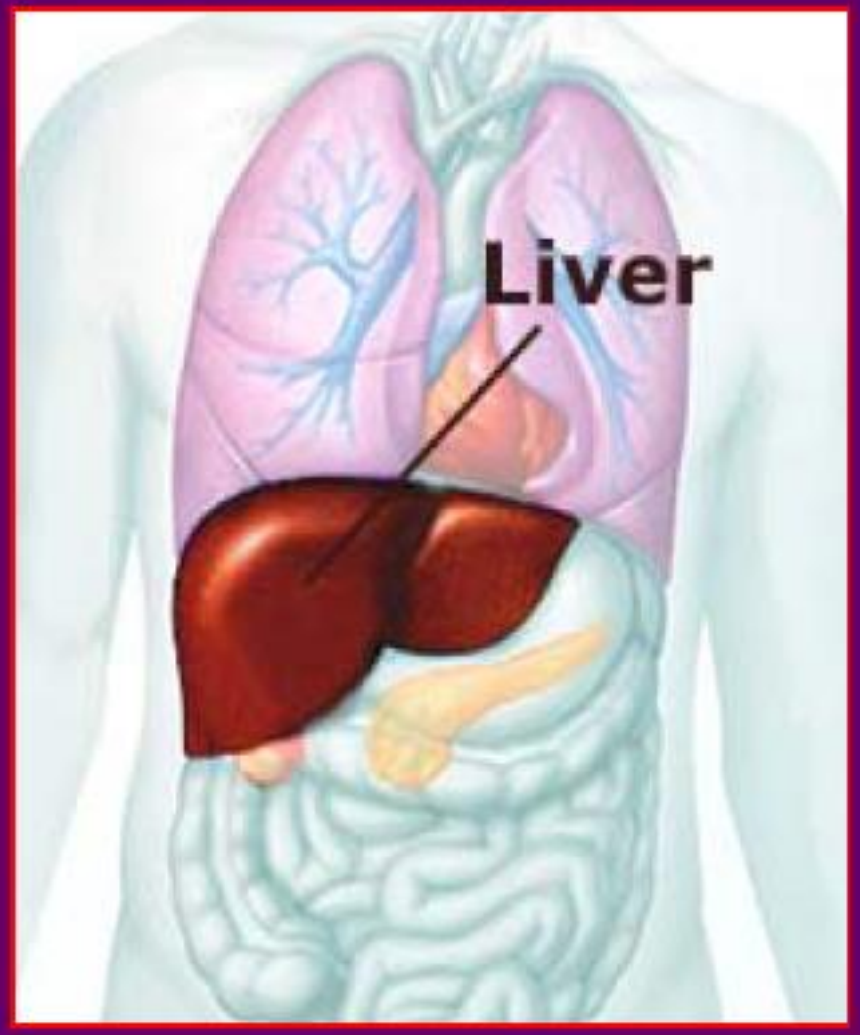
Plasma Specimen	No. of Positive Samples/ No. of Samples: Chiron NAT Assay	Roche AmpliScreen NAT Assay
Negative control	0/3	0/9
Positive control	3/3	9/9
Positive control, 1:16 dilution	3/3	9/9
Donor, undiluted	3/3	9/9

Transfusion-transmitted human immunodeficiency virus infection by a Danish blood donor with a very low viral load in the preseroconversion window phase

Screening Tests Introduced Since 1970



Hepatitis Viruses



Hepatitis B

Hepatitis B (HBV)

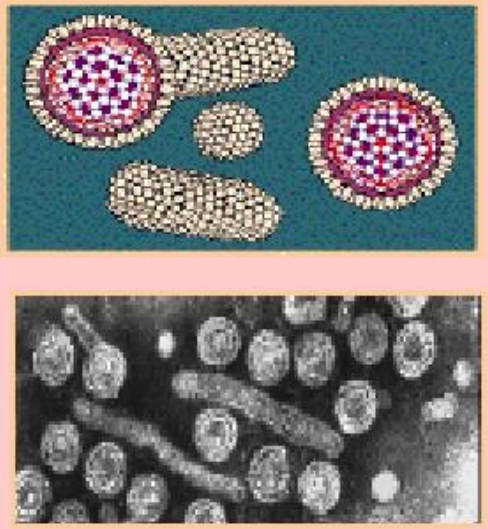
A virus that infects the liver

HBV can survive outside the body at room temperature for over 7 days

HVB is more easily spread than HIV

90% of adults contracting the disease recover fully and develop immunity

Up to 10% of adults contracting the disease become carriers



Courtesy, Linda Stannard, of the Department of Medical Microbiology, University of Cape Town

Hepatitis B Vaccine

A non-infectious, yeast-based vaccine

Prepared from recombinant yeast cultures, not from human blood products

No risk of developing HBV disease from the vaccine

The vaccine has been proven to be 90%+ effective

ENGERIX-B

Hepatitis B Vaccine

Manufactured by:

GlaxoSmithKline

Transfusion Transmitted Infections

Hepatitis

Hepatitis was the first documented transfusion-transmitted disease.

Many of the current practice for diminishing risk in transfusion medicine are based on the experience of controlling the transmission of hepatitis.

Hepatitis B virus

- The hepatitis B virus (HBV), a member of the Hepadnaviridae family,

✓**is capable of withstanding extreme temperatures and humidity.**

- Hepatitis B is a worldwide healthcare problem, especially in developing areas.
- An estimated one third of the global population has been infected with HBV.
- Approximately 300 million people are lifelong carriers, although annually, only 2% spontaneously seroconvert.
- In the United States, 300,000 cases of acute HBV disease are reported annually to the Centers for Disease Control and Prevention (CDC).[25]

Hepatitis B virus

- HBV is transmitted hematogenously and sexually.
- The outcome of this infection results from a complicated viral-host interaction that produces an acute symptomatic disease, an asymptomatic disease, or a chronic carrier state.
- Later consequences include cirrhosis and the development of hepatocellular carcinoma (HCC).
- **Note:** The residual risk of transmission of HBV is estimated to be close to 270,000 units in the United States and 1 in 70,000 to 1,000,000 units in various parts of Europe.[26]

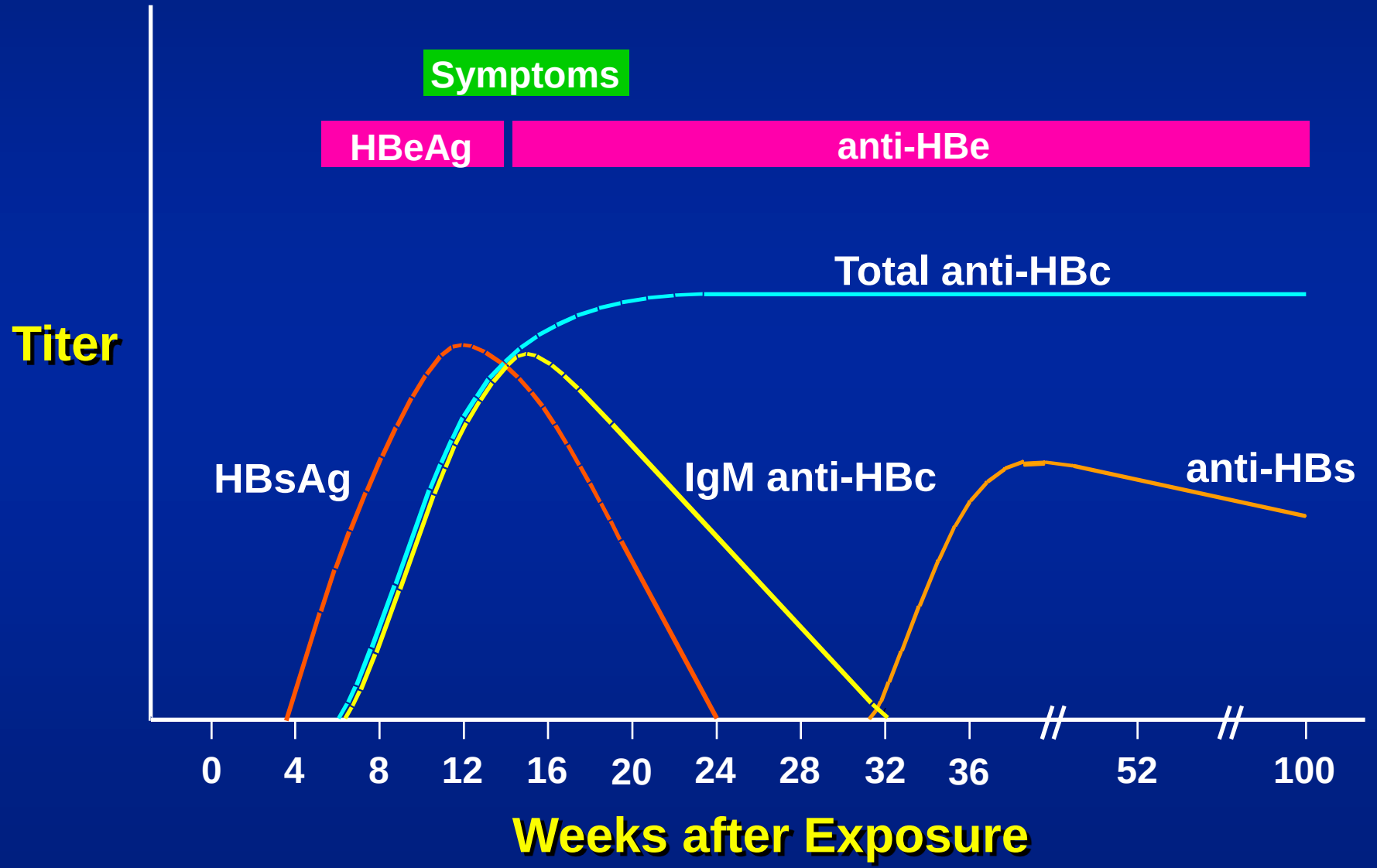
Transfusion Risks

Infections:

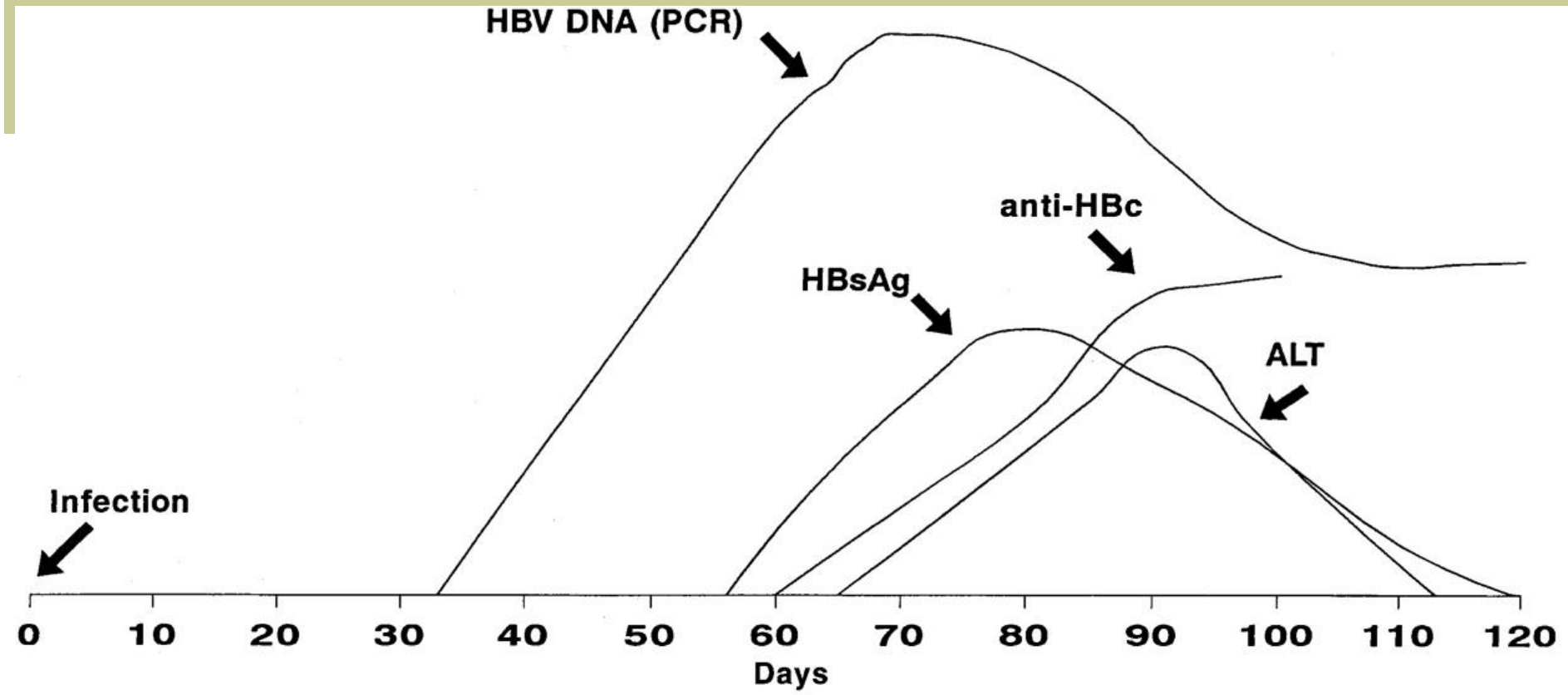
The known risks of transfusion-transmitted diseases are estimated as follows:

HIV (type I)	**1:1,800,000**
Hepatitis C	**1:600,000**
Hepatitis B	**1:220,000**

Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



HBV



Infection	Day 0
HBV DNA	Variable up to 23 days prior to HBsAg (average, 6-15 days)
HBsAg	Day 56; disappears Day 120

Hepatitis B virus

- Hepatitis B surface antigen (HBsAg) detection is a routine in many parts of the world.
- However, some chronic carriers have such a low viral load that screening by HBsAg may not be able to detect the infection in the donor.
- To overcome this obstacle, many blood banks in several countries also attempt to detect antibody against the hepatitis B core antigen (anti-HBcAg or anti-HBc).[27, 28]
- The core antibody develops early in the course of the infection and remains positive even in patients with low-level viremia.

Hepatitis B virus

- Hepatitis B poses another problem in some chronically infected people in whom HBV DNA is present in the blood products, but also in whom HBsAg is not detectable and anti-HBc is also equivocal.
- NAT has tremendous potential in this area of transfusion medicine.[21, 29, 30]
- Hepatitis B–positive donors are permanently deferred from giving blood.

HBV detection superiority with ID-NAT

Hepatitis B, hepatitis C and HIV transfusion-transmitted infections in the 21st century

Dwyre et al, Vox Sang 2011

D. M. Dwyre, L. P. Fernando & P. V. Holland
Department of Pathology, University of California Davis Medical Center, Sacramento, CA, USA

VoxSanguinis

REVIEW

[12]. Single-unit NAT testing can detect very low levels of HBV DNA (< 100 IU/ml). With the availability of multiplex testing of small pools of donor sera, more blood centres are implementing HBV NAT, along with HCV and HIV. However, without single-unit NAT HBV DNA testing, the window period may not be shortened that much, compared to the sensitive tests available today for HBsAg (like PRISM/Abbott Park, IL, USA). This can be explained by the relatively slower doubling time of HBV in the window period, resulting in a lower viral load. Thus far the consensus is that NAT should be used in conjunction with serological testing to identify low-level infections as well as infections that are at the ends of the window periods of detection.

Hepatitis C (HCV)

General Facts About Hepatitis C

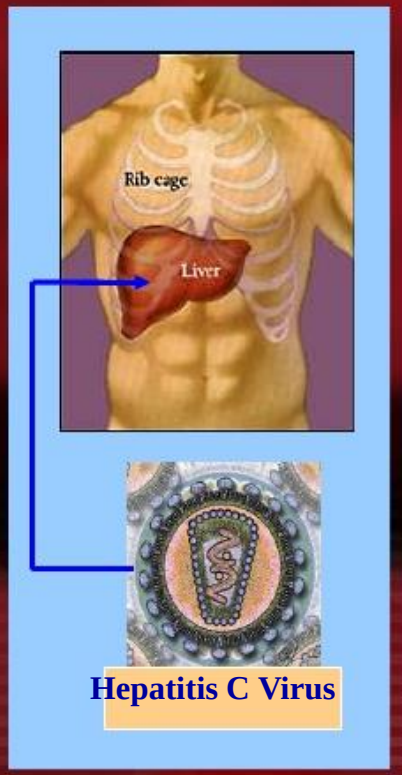
HCV was identified in 1989

One of the most common causes of chronic liver disease, cirrhosis and cancer

~ four million people affected in USA – with 180,000 new infections annually

8,000-10,000 HCV annual deaths in USA

Globally ~ 170 million chronic infections



Hepatitis C virus

- The hepatitis C virus (HCV) is a spherical, enveloped, single-stranded RNA virus belonging to the Flaviviridae family.
- The World Health Organization (WHO) estimates that 170 million individuals worldwide are infected with HCV, with a wide variation in the prevalence of the disease.
- For example, in 2000, Frank et al reported that Egypt had the highest number of reported HCV infections, largely attributed to the use of contaminated, parenteral, antischistosomal therapy.[35]
- This led to a mean 22% prevalence of HCV antibodies in persons living in Egypt.
- According to the CDC, an estimated 1.8% of the US population is positive for HCV antibodies.[23, 27, 36]

Hepatitis C (HCV)

Most commonly occurs in people who have:

- received blood transfusions before 1992
- shared needles
- had tattoos
- had body piercing

Risk of sexual transmission appears to be small

No evidence that it can be transmitted by casual contact, through foods, or by coughing or sneezing

Transmission from mother to child appears to be uncommon

Hepatitis C (HCV)

The virus is very robust.

The virus can remain undetected in the body for years

HCV may be identified after 5 - 8 weeks from exposure in approximately 60% of infected persons

Most Hepatitis C infections (80-90%) become chronic and lead to liver disease and liver failure

There is no vaccine for Hepatitis C

Hepatitis C virus

- HCV is predominantly transmitted by means of percutaneous exposure to infected blood. In developed countries, most new HCV infections are related to intravenous (IV) drug abuse and are found because of intensive screening and look back programs.
- Blood transfusion was a major risk for acute HCV infection in the past, with more than 10% of transfusion recipients acquiring the infection in some studies.[26]

Hepatitis C virus

- The screening of blood donors by donor history and elevated serum alanine aminotransferase (ALT) caused a striking reduction of non-A, non-B posttransfusion hepatitis, even before HCV was identified.
- The subsequent initiation of donor screening for anti-HCV antibodies in 1990 nearly eliminated the risk of post transfusion acute HCV infection.[26]

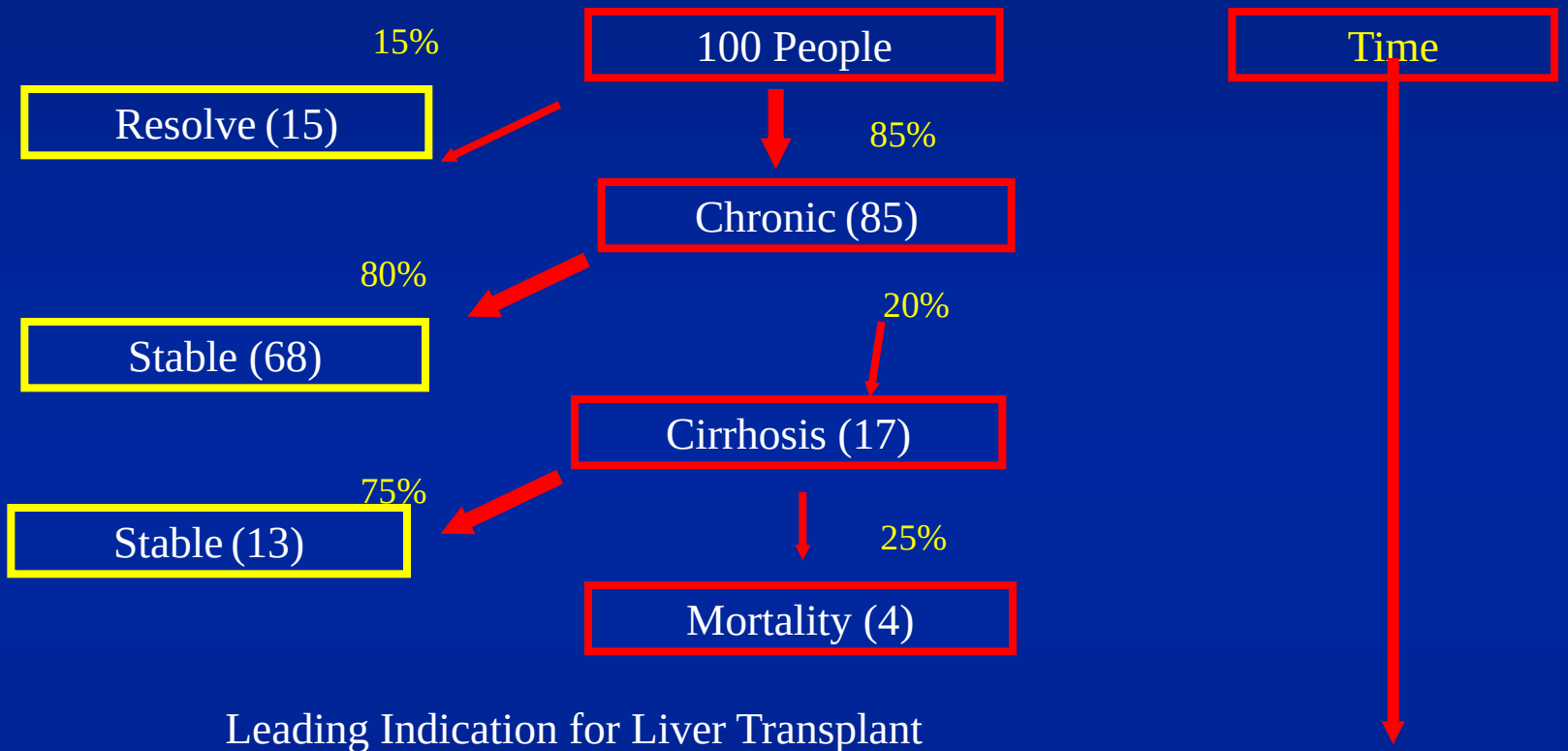
Hepatitis C virus

- Indeed, such screening has decreased the risk of transfusion-associated HCV infection to less than 1 case in 103,000 transfused units.[19, 20, 21, 36]
- Detection of HCV infection by MP-NAT is the standard of care in the United States for the detection of the viral RNA.
- The HCV MP-NAT has reduced the window period for the detection of infection by 80-90% when compared with HCV testing by detection of antibodies.[22]

Hepatitis C virus

- The use of the polymerase chain reaction (PCR) assay has reduced the risk of acquiring HCV from blood transfusions to 1 in 230,000 donations.
- The newer assays have decreased the window period after infection to 1-2 weeks.
- Hepatitis C–positive donors are permanently deferred from blood donations.

Natural History of HCV Infection

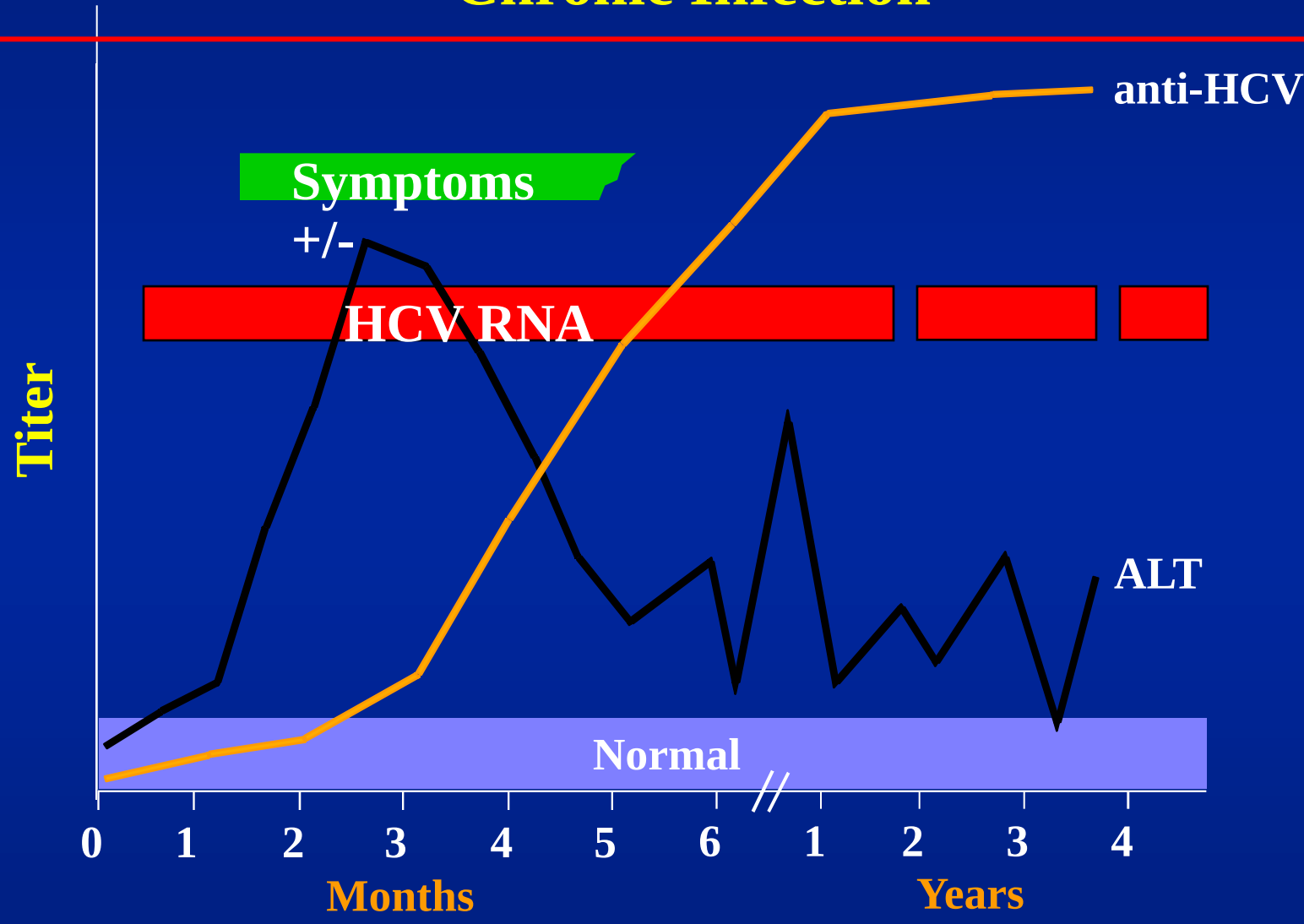


Leading Indication for Liver Transplant

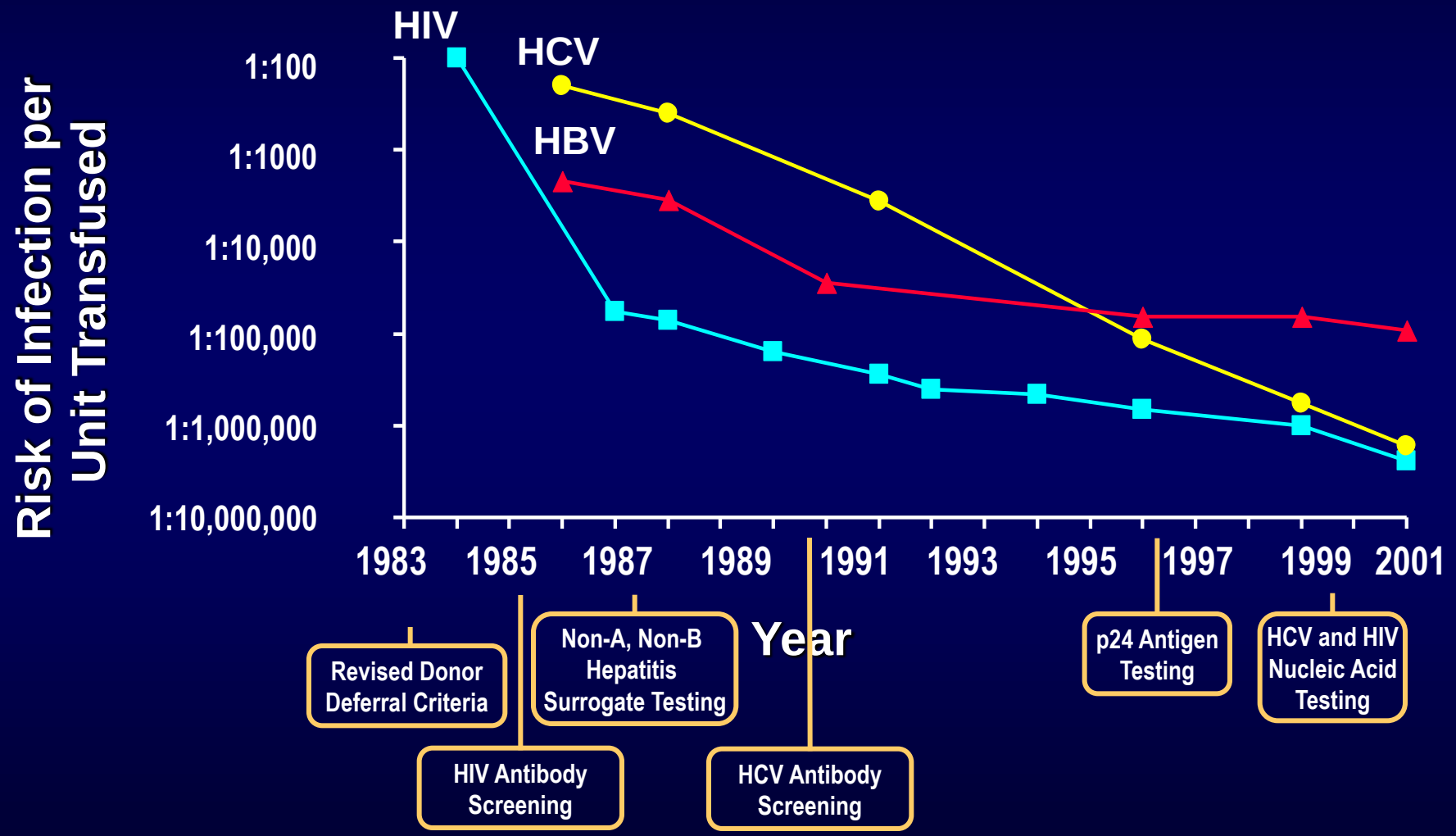
Note: This slide shows the number of people that progress on so mild, moderate and severe HCV disease.

Adapted from Alter HJ

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Decline in HIV, HBV, HCV Risks of Transmission via Blood Tx



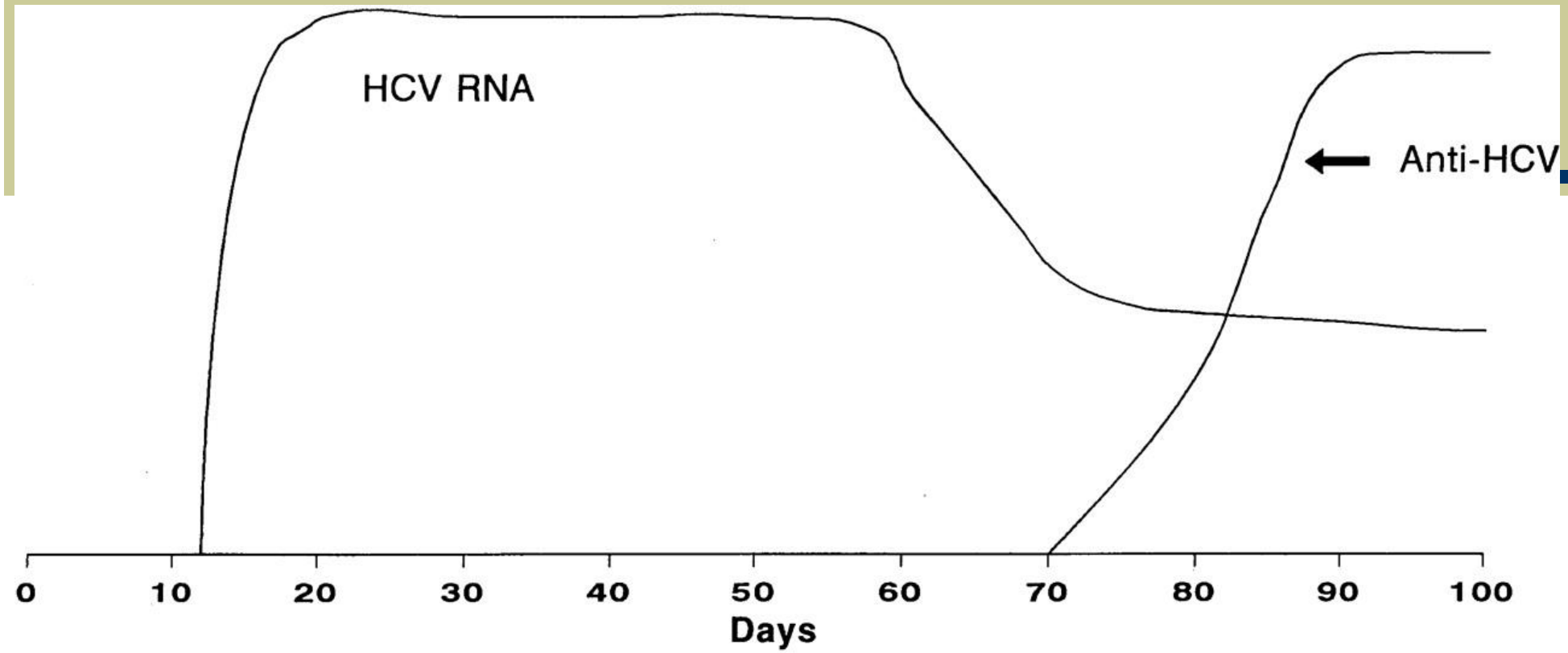
Busch MP, et al. *JAMA.* 2003;289:959-62.

Risks of Transfusion: Infectious Disease

- ✓ HIV = 1 in 1.8 million
- ✓ HCV = 1 in 1.6 million
- ✓ HBV = 1 in 220,000

HIV = human immunodeficiency virus.
HCV = hepatitis C virus.
HBV = hepatitis B virus.
Busch MP, et al. *JAMA.* 2003;289:959-62.

HCV



Infection	Day 0
HCV RNA	Day 12
HCV Antibody	Day 70

There is a Long Lag to Screening Assay

Agent	Recognized as a Transfusion Risk	First Screening Assay	Interval (year)
HBV	1940	1970	30
HCV	1975	1990	15
HIV	1982	1985	3
WNV	2002 (1999)*	2003	1 (4)
Chagas	2002	2007	5
Bacteria	1986	2004	18

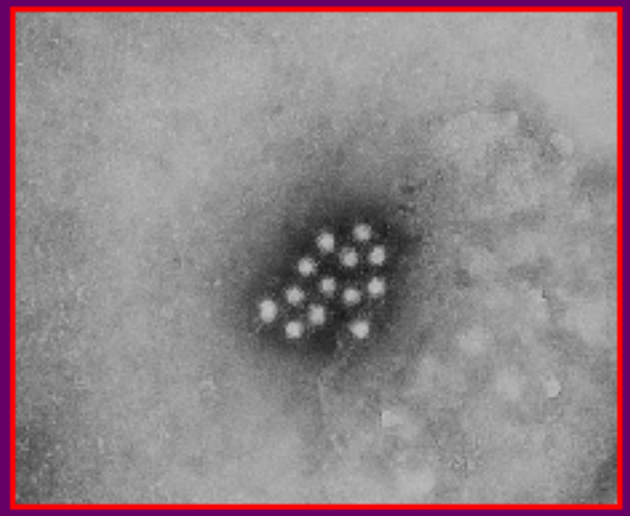
** Suspected, but not proven, in 1999*

Hepatitis A and E viruses

- The hepatitis A virus (HAV) is a single-stranded RNA enterovirus and a member of the Picornaviridae family.
- In humans, viral replication depends on hepatocyte uptake and synthesis, and assembly occurs exclusively in liver cells. The common method of HAV transmission is via the feco-oral route, but the infection may also rarely be transmitted through blood transfusion.[31, 32]
- The hepatitis E virus (HEV) is classified in the Caliciviridae family and has many similarities with HAV.
- The common mode of transmission is also feco-oral, but HEV may also be transfusion transmitted.[33, 34]
- Both of these nonenveloped viruses are not inactivated by the methods used in the production of blood components subjected to plasma fractionation and processed by solvent and detergent methods alone.[31, 32, 33, 34]

Hepatitis A Virus (HAV)

- ***Hepatitis A virus***
  Virus classification
- Group:Group IV ((+)ssRNA)
- Family:*Picornaviridae*
  Genus:*Hepatovirus*
  Species:***Hepatitis A virus***



TEM micrograph of hepatitis A virions.

Transfusion Transmitted Infections

In 2002, as mosquitoes carried **West Nile virus** across the USA, infecting 4200 people, 23 confirmed cases of TTI and 7 related death were reported.

This was a dramatic demonstration that

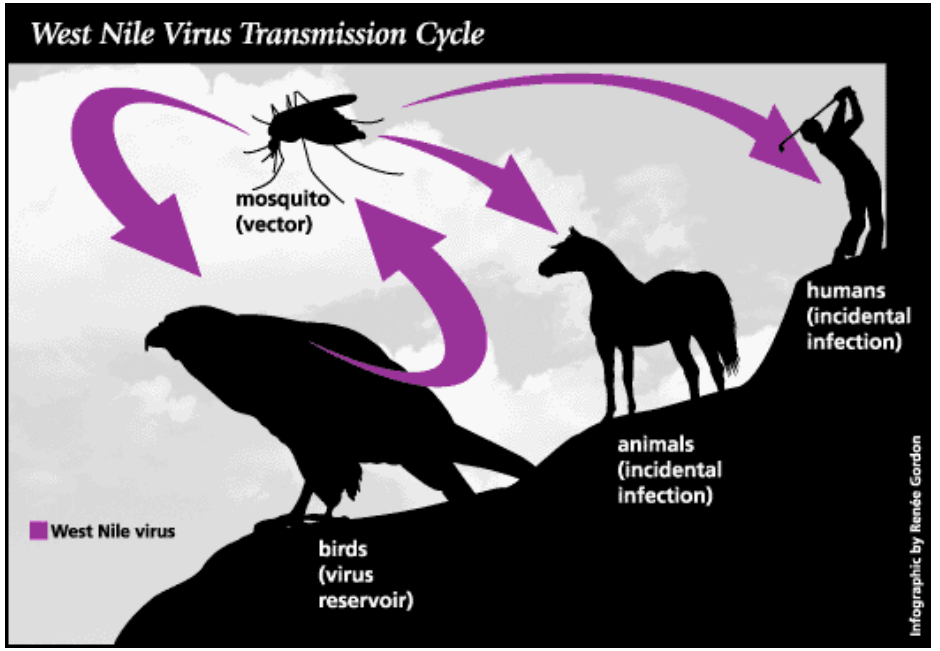
an emerging agent can threaten the safety of the blood supply.

West Nile virus

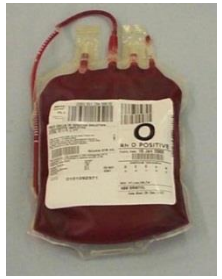
- The West Nile virus (WNV), a flavivirus, is transmitted by mosquito bite.
- The organism has the potential of being transmitted through blood.
- The infection is usually asymptomatic and goes undetected, but it may cause meningoencephalitis, especially in individuals who are older and who have depressed immunity, with a mortality rate of about 2.6%.
- In 2002, there were about 9858 cases of WNV infection reported to the CDC.[37, 38]

West Nile Virus (WNV)

- Flavivirus
- Most cases asymptomatic
- very mild short term symptoms (20% infections)
- 1% encephalitis/meningitis; can be fatal
- First identified 1937 W Nile area Uganda
- widely distributed Africa, West Asia, Europe & Australia; US since 1999



transmission may occur as a result of blood donation



- The current strategy to break the chain of WNV transmission via blood is NAT.
- An intriguing situation is the high risk of residual transmission in some early phase viremic patients.
- Thus, NAT is used on individual donor samples (ie, individual donation nucleic acid testing [ID-NAT], instead of pool testing [ie, MP-NAT]) to detect these low-level viremic patients.
- This is especially useful to interdict transmission in the high-incidence season.
- For donors who are detected as positive for WNV infection, the US Food and Drug Administration (FDA) recommends deferral for at least 120 days.[42, 43, 44, 45]

Cytomegalovirus

- The transmission of cytomegalovirus (CMV), which belongs to the herpes group of viruses, is well documented throughout the literature.
- The organism's transmission is prevented by transfusing leukocyte-depleted blood products, which is consistent with the fact that CMV is a leukocyte-associated pathogen.
- The organism is a major concern when it comes to transfusing immunocompromised hosts.
- For this reason, all immunocompromised patients are given CMV-seronegative or leukocyte-depleted blood products.[46, 47, 48, 49]

Human T-cell lymphotrophic virus

- Human T-cell lymphotrophic virus–1 (HTLV-1) and HTLV-2 have been shown to be transmitted by blood transfusion.
- The residual risk of transmission is 1 in 3 million in the United States.
- Infection with these retroviruses may result in HTLV-related myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia/lymphoma.
- Various laboratories test for the presence of these agents by different serologic or nucleic acid–based tests, including enzyme immunoassay (EIA) and PCR assay.[50, 51, 52, 53]

Parvovirus B19

- Parvovirus is a nonenveloped virus that is usually transmitted by the respiratory route and that eventually infects hematopoietic cells.
- The virus is also transmitted vertically from mother to child and via blood products.
- Transmission by blood products is common because the virus does not have a lipid envelope, rendering inactivation methods (eg, using methylene blue or the solvent-detergent method) ineffective.[54]

- The spectrum of clinical results of parvovirus infection depends mainly on the immune status of the recipient.
- The parvovirus may cause bone marrow failure in immunocompromised patients and patients with sickle cell disease. In the immunocompromised host, the disease is self-limited, without subsequent complications.
- As stated, pregnant women can transmit the virus vertically to the fetus, leading to fetal hydrops (heart failure).[55, 56]
- This is of importance considering the fact that many pregnant women receive RhoGAM (anti-D immunoglobulin; Ortho-Clinical Diagnostics, Inc, Raritan, NJ) to prevent sensitization by fetal antigens.
- PCR assay–based tests are being developed to counteract this problem.[57]

Other viruses

- Hepatitis G virus (HGV) and transfusion-transmitted virus (TTV) also have been shown to be transmissible via blood.
- The clinical impact of their transmission on a larger scale has still to be deciphered.[58, 59]

Prion Diseases

- Two forms of Creutzfeldt-Jakob disease (CJD) have been reported in the literature; namely, classical CJD and variant CJD (vCJD).
- The latter, vCJD, is a form of human bovine spongiform encephalopathy (BSE) that is transmissible through consumption of infected tissues or potentially via blood transfusions.
- Initially, there was evidence of vCJD transmission through blood transfusion in animal studies, and cases in which the prion disease resulted from the administration of blood products have been reported from high-prevalence areas in Europe.

- An interesting fact to note is that people who have had transfusion-transmitted vCJD did not receive leukocyte-depleted blood.
- The prolonged asymptomatic phase and carrier states present a unique challenge with respect to prion disease in the context of transfusion medicine.
- In order to counteract this problem, donor deferral becomes critical.
- Donors in high-prevalence countries in Europe are being deferred permanently if they themselves received blood products after 1980.[69, 70, 71, 72, 73]

Human Immunodeficiency Virus (HIV)

Screening tests on donated blood units (Mandatory In Iran)

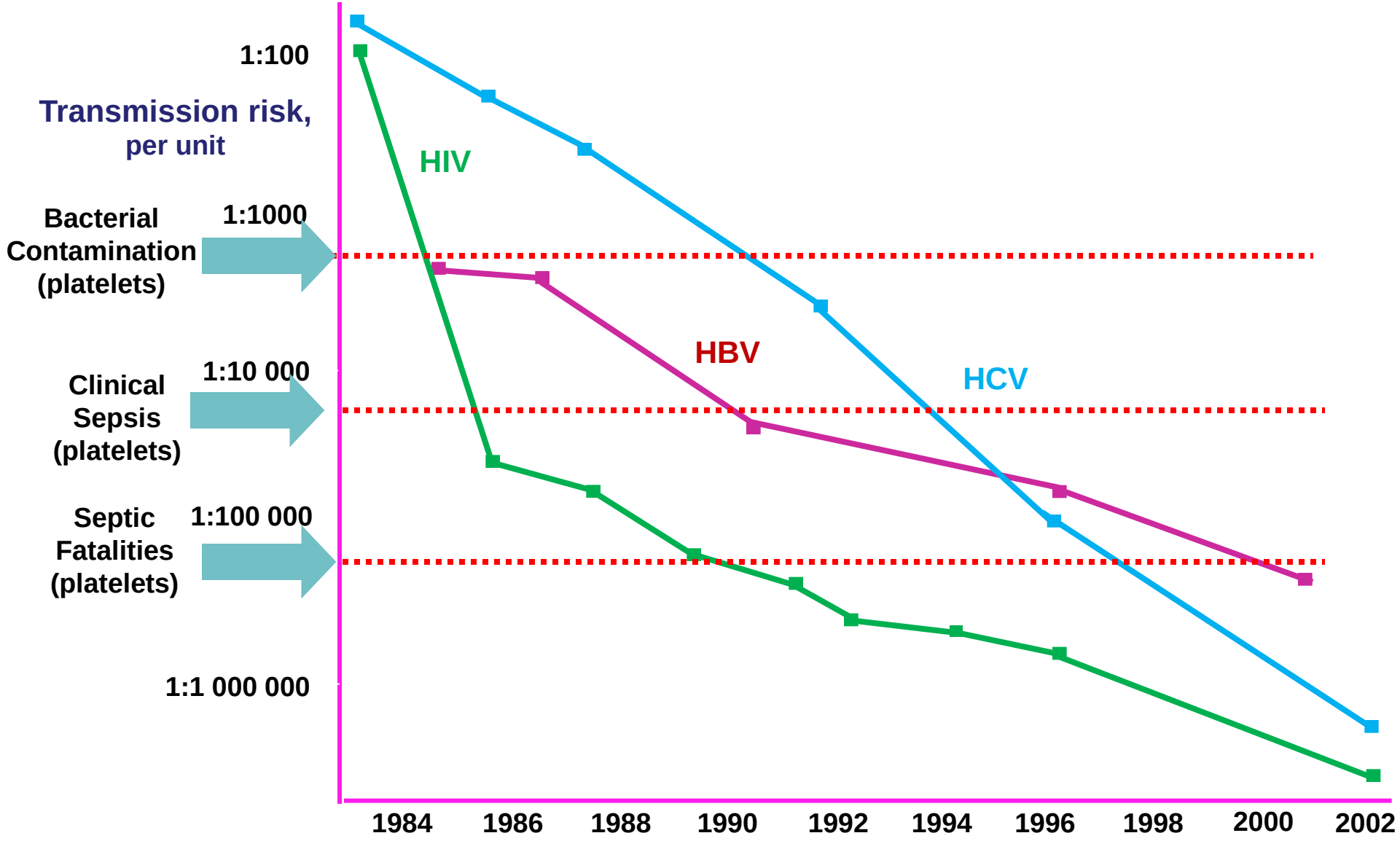
- HBsAg
- HCV Ab
- HIV Ab
- RPR

Human Immunodeficiency Virus (HIV)

Screening tests on donated blood units (Mandatory In Iran)

- HBsAg
- HCV Ab
- HIV Ab
- RPR

Comparison of Residual Risks



Updated from: Goodnough LT *e t al. NEJM* 1999;341:126-7

Screening of donated blood

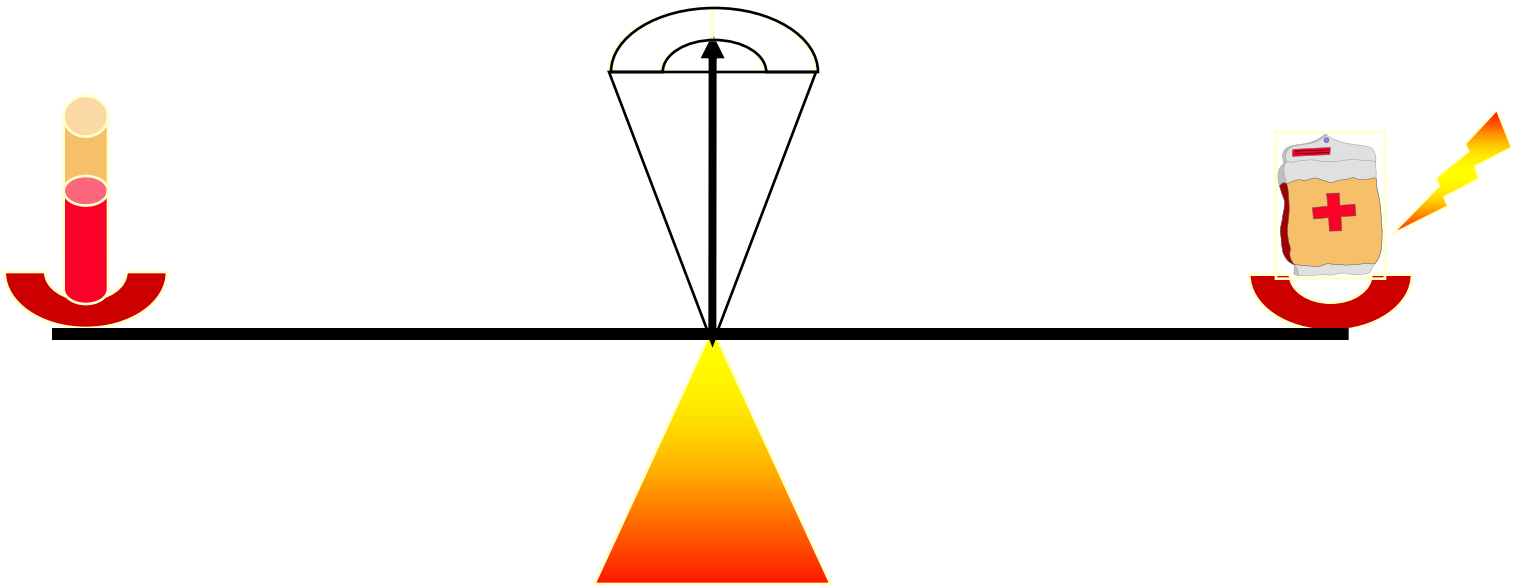
- After donation, each unit of donated blood undergoes a series of tests for the following:
- HBV and HCV
- HIV-1 and HIV-2
- HTLV-1 and HTLV-2
- Syphilis
- *T cruzi*
- **Note:** Apheresis platelets are also tested for bacterial contamination.

Current Pathogens of Concern for Blood Operators

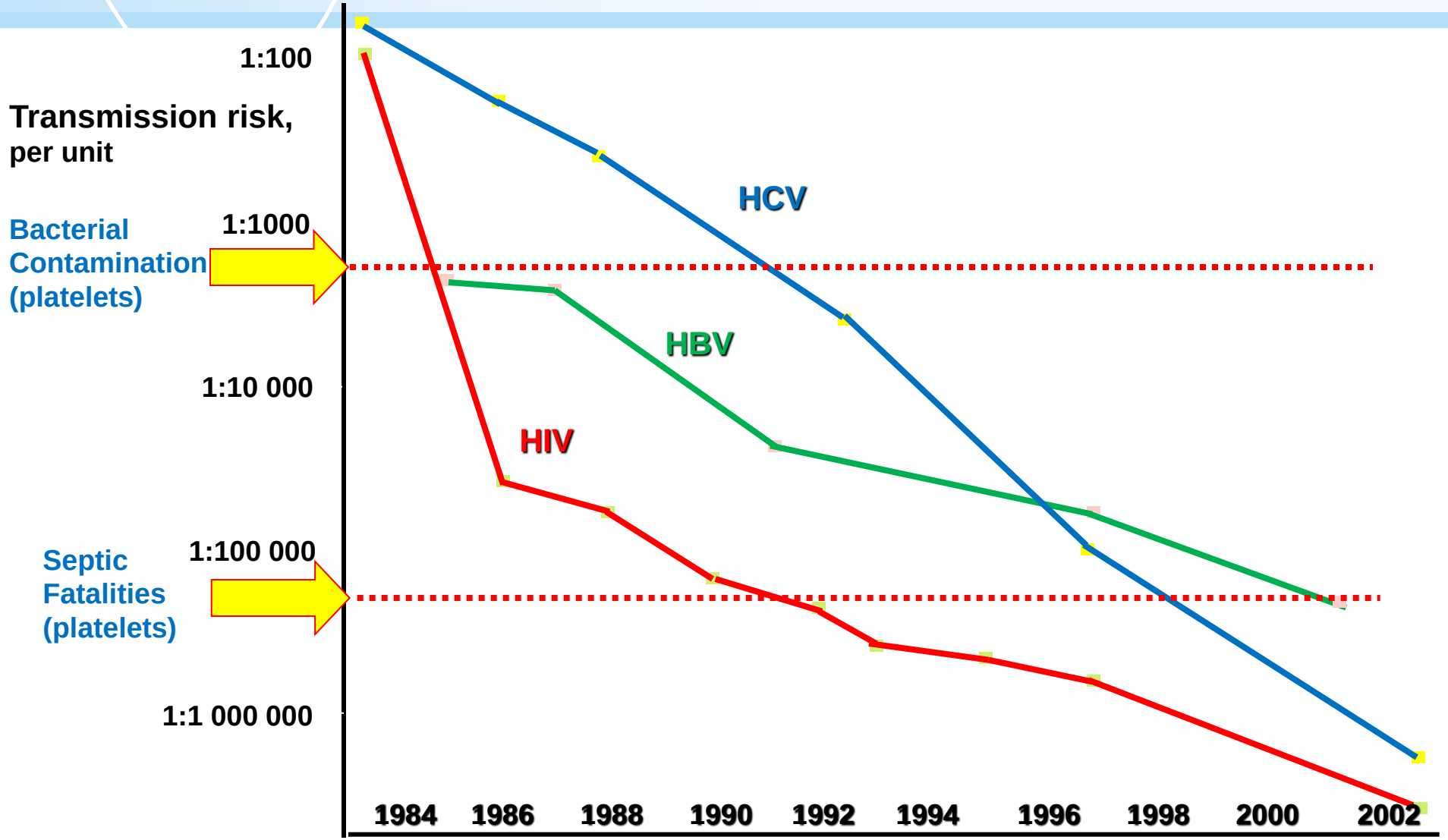
- **Chagas Disease** - protozoan
- **Babesiosis** - protozoan
- **vCJD** (variant Creutzfeld Jacob Disease) – prion
- **Influenza** - virus
- Malaria - protozoan
- Ehrlichiosis – bacteria
- HHV8 - virus
- Dengue - virus

Blood Safety Strategies

Testing vs. Inactivation

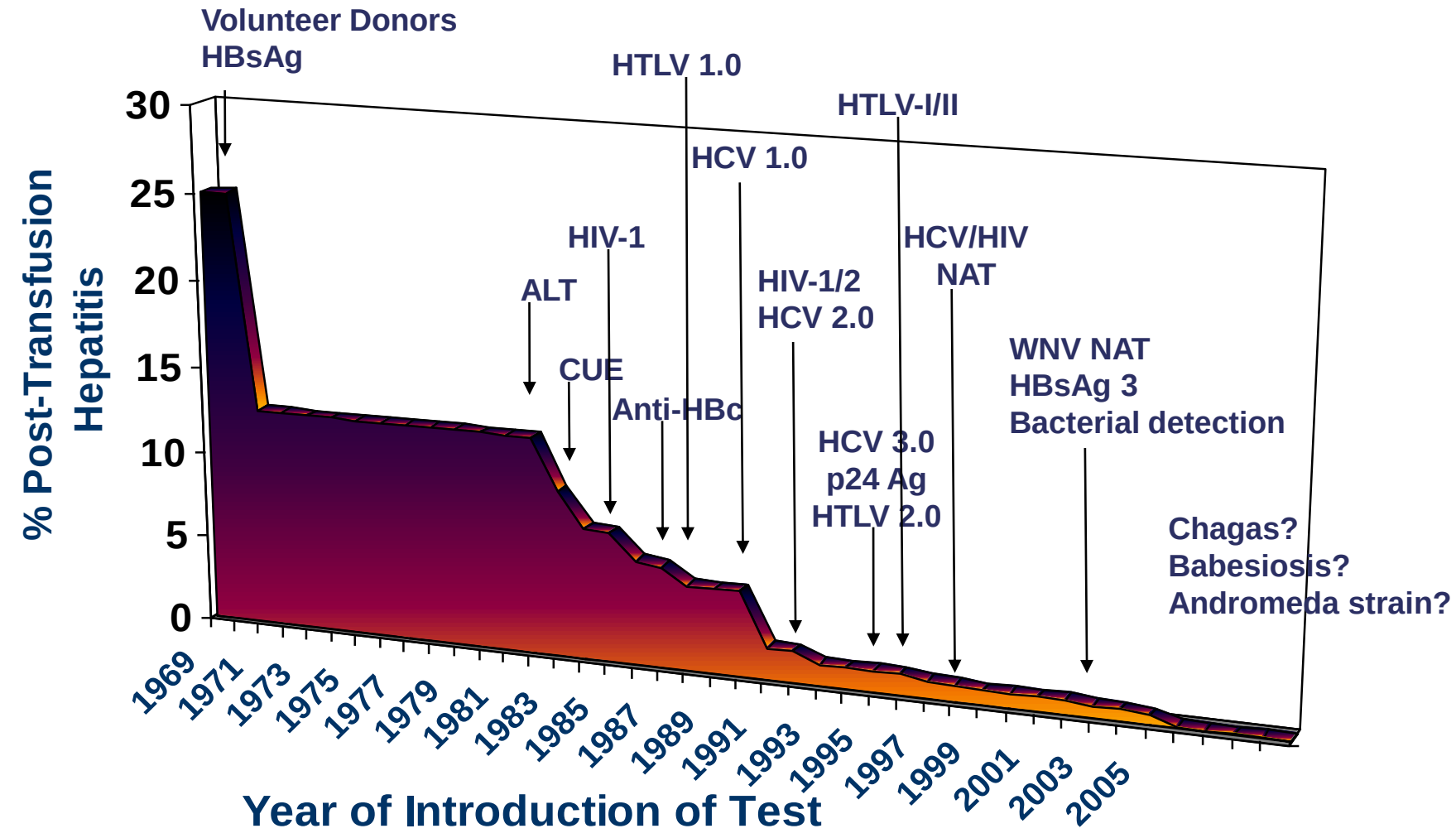


Residual Risk of TT-HIV/HBV/HCV Reduced



Updated from: Goodnough LT *et al. NEJM* 1999;341:126-7

Impact of Viral Testing on Safety



After H. Alter

Historical perspective

- Pre-1985: syphilis, HBsAg
- 1985-1989: better HBsAg, HIV, HTLV,
  + ALT, anti-HBc (surrogates for nonA, nonB Hep)
- 1990: added HCV, HIV-2, HTLV-II
- 1996: HIV p24 Ag testing
- 1999: HIV, HCV NAT
- 2004: WNV NAT

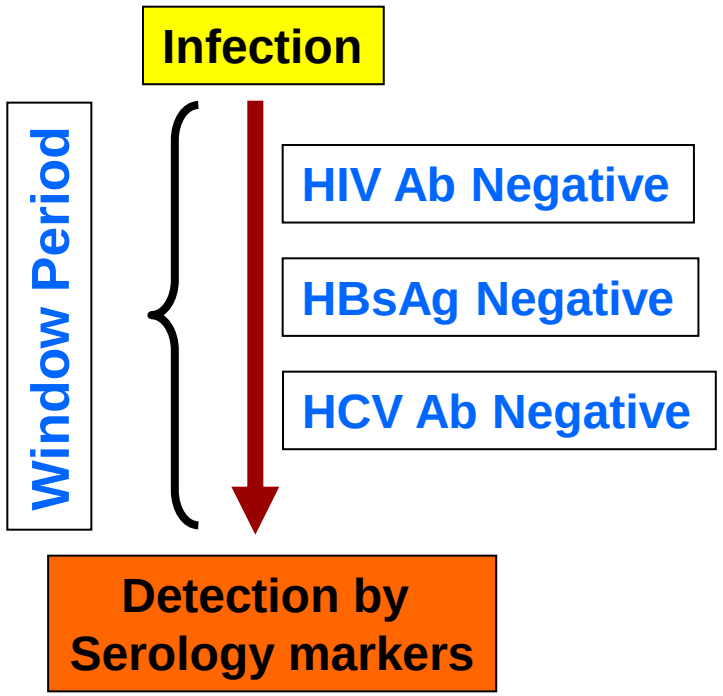
Transfusion – Associated Infections

- In addition to **WNV**, mosquito-borne pathogens, such as **dengue** and **chikungunya** viruses, have shown potential for transfusion transmission, although the burden of disease is unknown.
- Tick-borne agents also are recognized to pose an increasing risk to transfusion safety, including transmission of babesiosis and, most recently, **anaplasmosis** and **ehrlichiosis**.
- Transmission of variant **Creutzfeldt-Jakob disease (vCJD)** via transfusion has occurred in the United Kingdom.

SCOPE OF BLOOD TRANSFUSION

- Of the 164 countries providing data to the WHO, 39 were not able to screen all of their donated blood for one or more of the four infections (**HIV infection**, **hepatitis B**, **hepatitis C**, and **syphilis**) that are most widely recognized to be transmitted through blood and are recommended by the WHO to be screened at donation.
- A total of 106 countries have national guidelines on the appropriate clinical use of blood, whereas 57 countries have a national hemovigilance system to monitor adverse events associated with transfusion.[8,9]

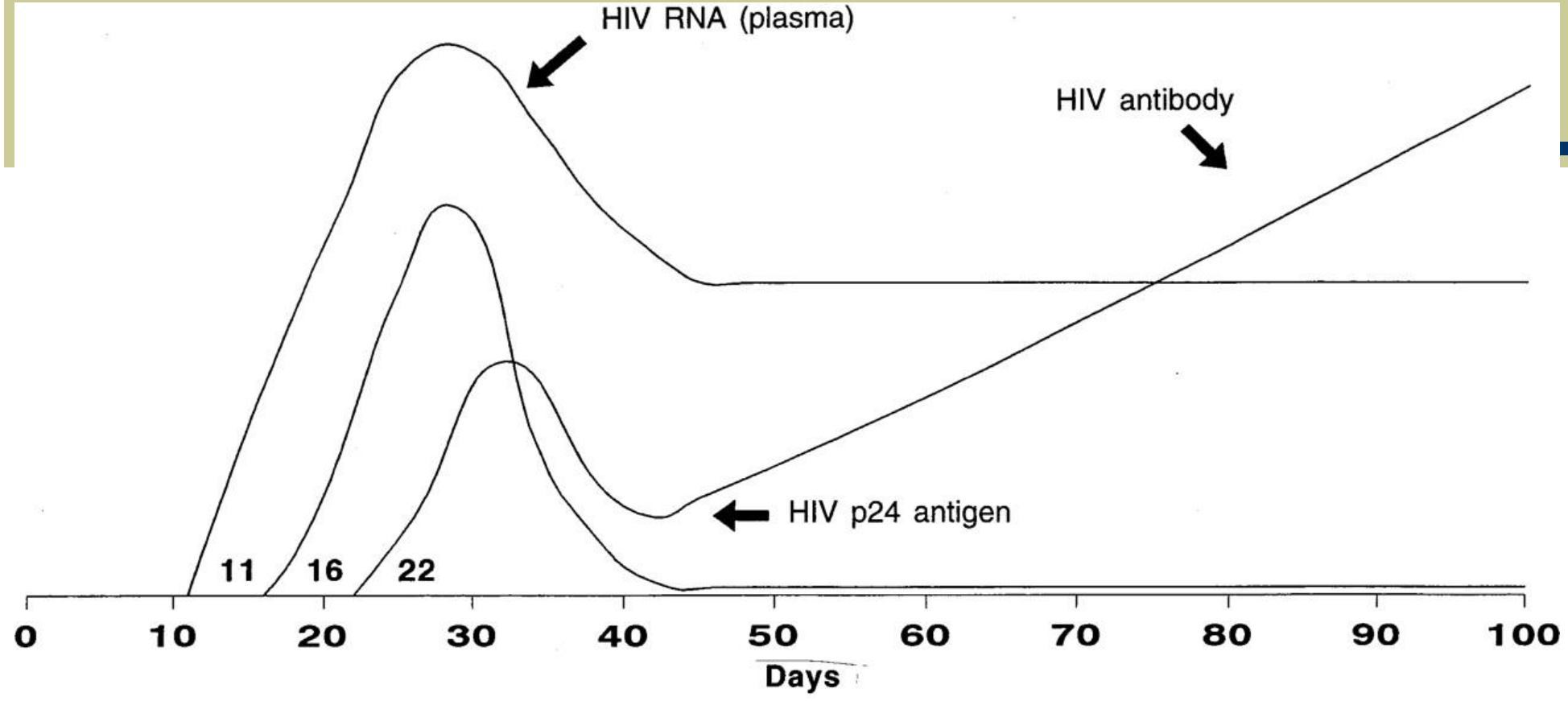
Window Period



HIV

- Short doubling time of 21 hours
- Window period of 16 days (p24 antigen) may be reduced to 11 days by NAT

HIV



Theoretical Infectivity

Day 0

HIV RNA — **Day 11**

HIV p24 antigen — **Day 16**

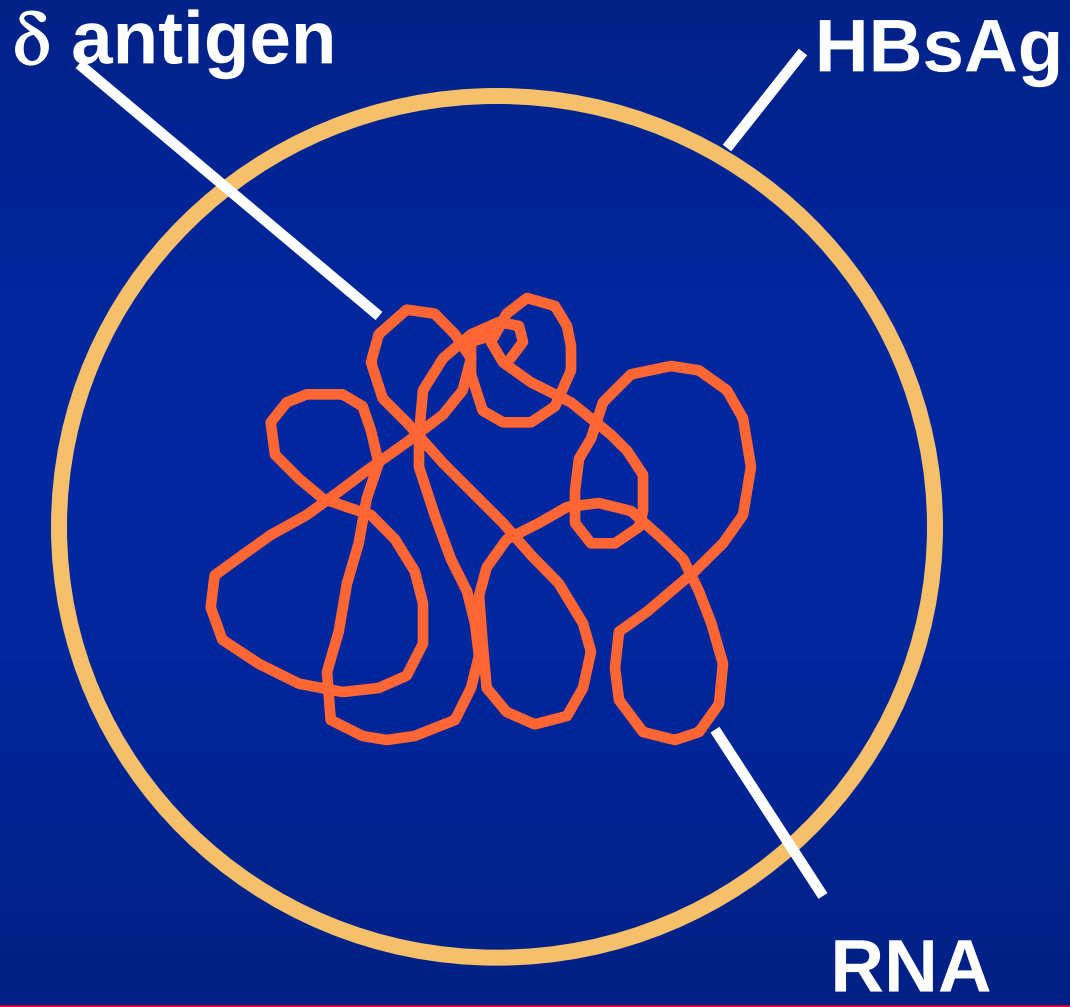
HIV antibody — **Day 22**

5 Days

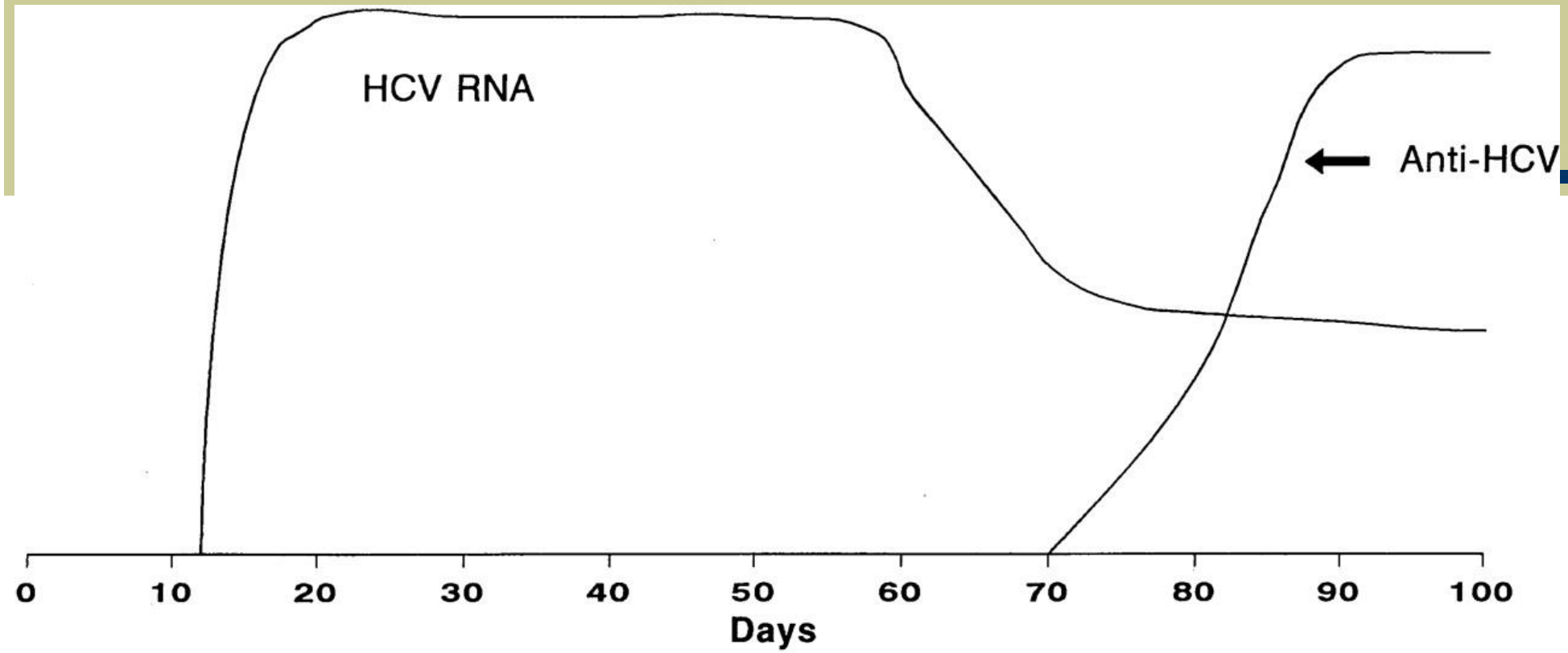
6 Days

11 Days

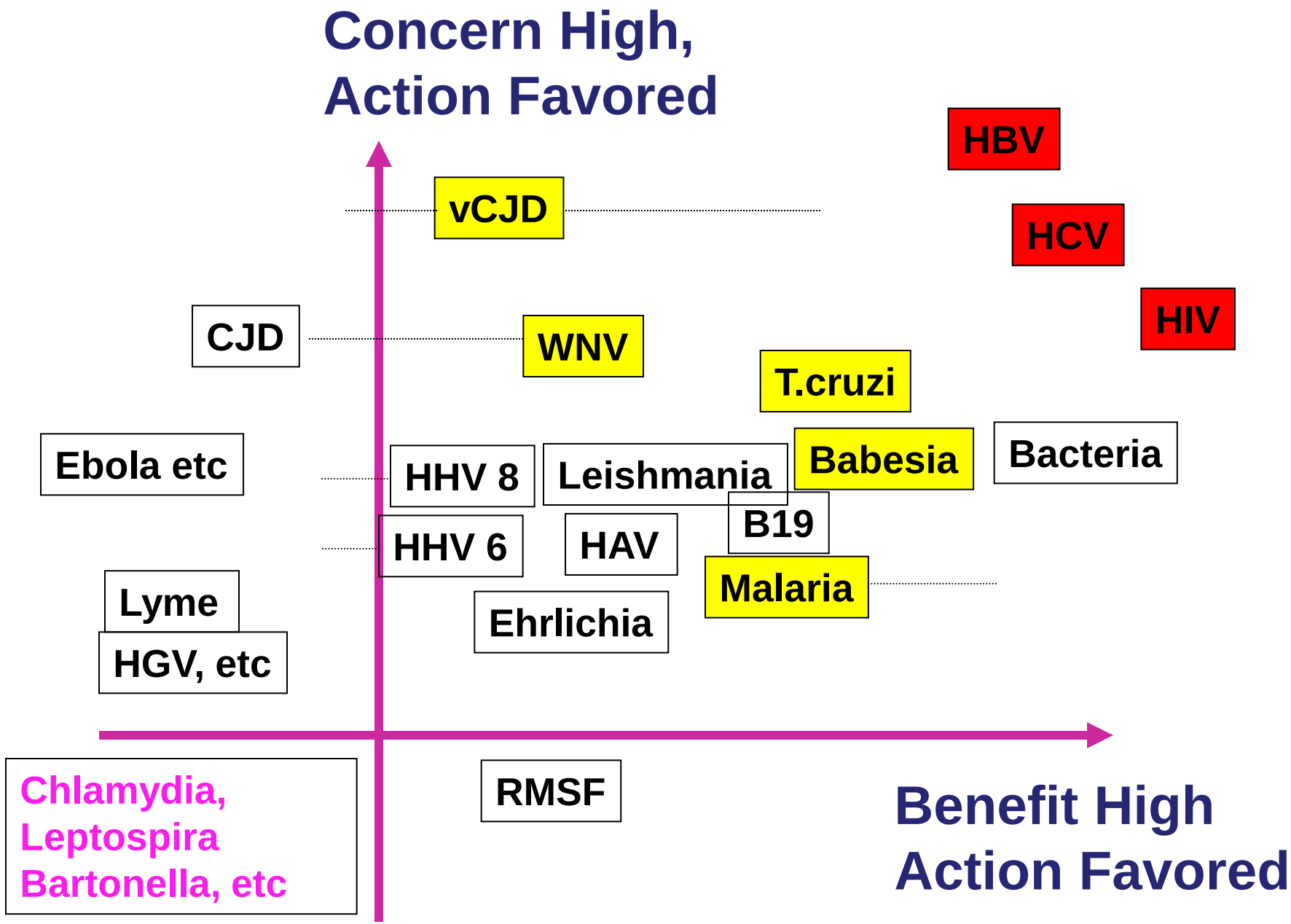
Hepatitis D (Delta) Virus



HCV



Infection	Day 0
HCV RNA	Day 12
HCV Antibody	Day 70


Concern High,
Action Favored
HBV
vCJD
HCV
HIV
CJD
WNV
T.cruzi
Ebola etc
HHV 8
Leishmania
Babesia
Bacteria
B19
HHV 6
HAV
Malaria
Lyme
Ehrlichia
HGV, etc
Chlamydia,
Leptospira
Bartonella, etc
RMSF
Benefit High
Action Favored

Transfusion Transmitted Infections

In 2002, as mosquitoes carried **West Nile virus** across the USA, infecting 4200 people, 23 confirmed cases of TTI and 7 related death were reported.

This was a dramatic demonstration that

an emerging agent can threaten the safety of the blood supply.

Transfusion – Associated Infections

- As we manage to control the known threats,
  however, new challenges
  will continue to arrive.

BLOOD IS A PRICELESS GIFT.....

.....but the final product costs !!

Family:*Retroviridae*
Genus:*Lentivirus*

- **Virus classification**
  Group:Group VI (ssRNA-RT)
- **Species**
- ***Human immunodeficiency virus 1***
- ***Human immunodeficiency virus 2***

Human T-Cell Leukemia Virus (HTLV)

- **HTLV was discovered in 1977 in Japan. The virus was first isolated by Drs. Bernard Poiesz and Francis Ruscetti and their co-workers in the laboratory of Robert C. Gallo at the NCI. It was the first identified human retrovirus.**
- **HTLV-I** is also called the **human T-cell lymphotrophic virus**, a virus that has been seriously implicated in several kinds of diseases including HTLV-I-associated myelopathy,

HTLV-1

- Transmission of HTLV-I is believed to occur from mother to child; by sexual contact; and through exposure to contaminated blood, either through blood transfusion or sharing of contaminated needles. The importance of the various routes of transmission is believed to vary geographically.

HTLV-II

- A virus closely related to HTLV-I, HTLV-II shares approximately 70% genomic homology (structural similarity) with HTLV-I.
- It is found predominantly in IV drug users and Native Americans, as well as Caribbean and South American Indian groups.
- HTLV-II has not been clearly linked to any disease, but has been associated with several cases of myelopathy/tropical spastic paraparesis (HAM/TSP)- like neurological disease.

HTLV-III and HTLV-IV

- The terms "HTLV-III" and "HTLV-IV" have been used to describe recently characterized viruses.

- These viruses were discovered in 2005 in rural Cameroon, and were apparently transmitted from monkeys to hunters of monkeys through bites and scratches. HTLV-III is similar to STLV-III (*Simian T-lymphotropic virus 3*), but HTLV-IV does not resemble any known virus. It is not yet known how much further transmission has occurred among humans, or whether the viruses can cause disease.

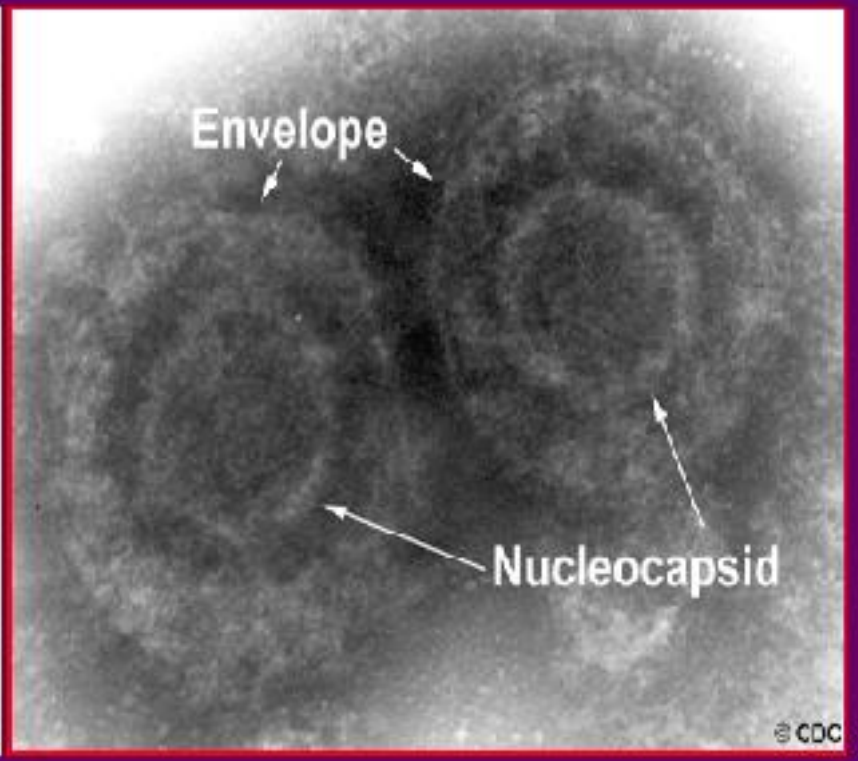
- *The use of these names can cause some confusion, because the name HTLV-III was the former name of HIV in early AIDS literature, but has since fallen out of use. Also, the name HTLV-IV has been used to describe HIV-2.*

- HHV 6 (Human Herpes Virus type 6) Roseala Infantum
- HHV 8 (Human Herpes Virus type 8) Kaposi's Sarcoma
- HPV B 19 (Human Papilloma Virus type B 19) Exanthema subitum

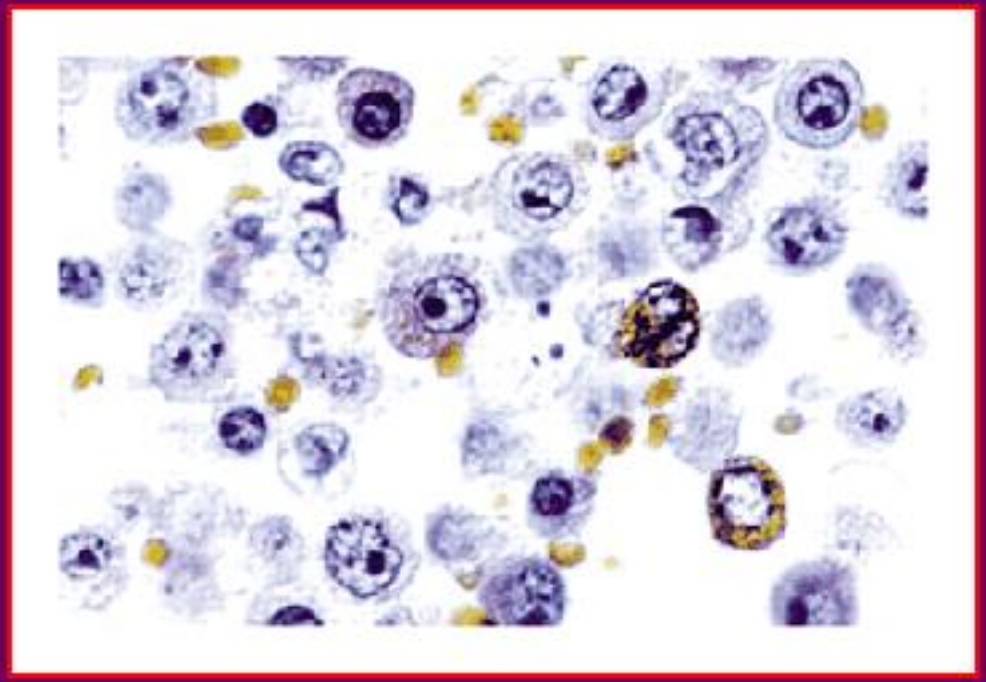
HHV 6

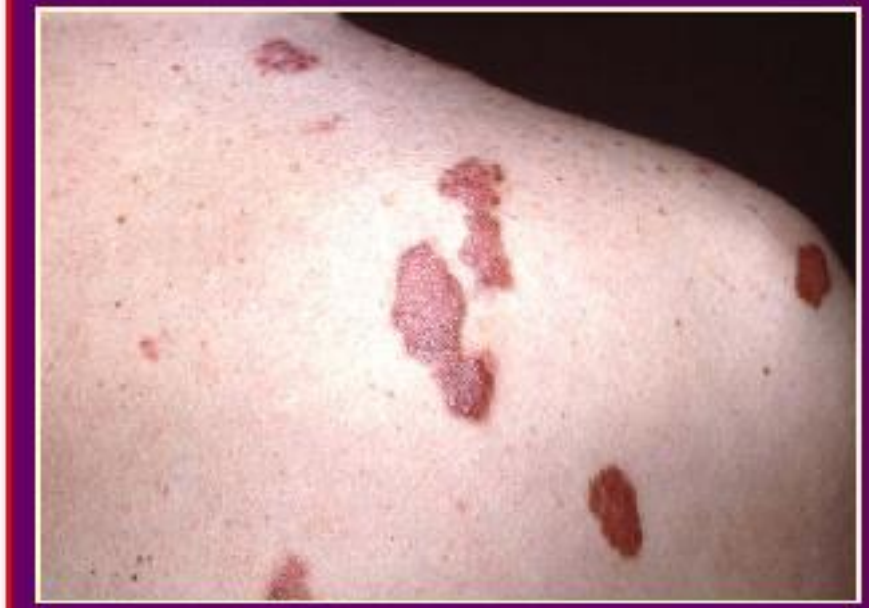
- HHV-6 is thought to be present in ≤95% of the human population.
- Primary HHV-6 infection takes place by age 2 and usually presents as an unremarkable febrile illness, although some children will develop roseola infantum.
- The peak age of infection is 6-9 months, with a mean duration of illness of 6 days.

HHV 6 & Roseola infantum



HHV 8 & Kaposis's Sarcoma



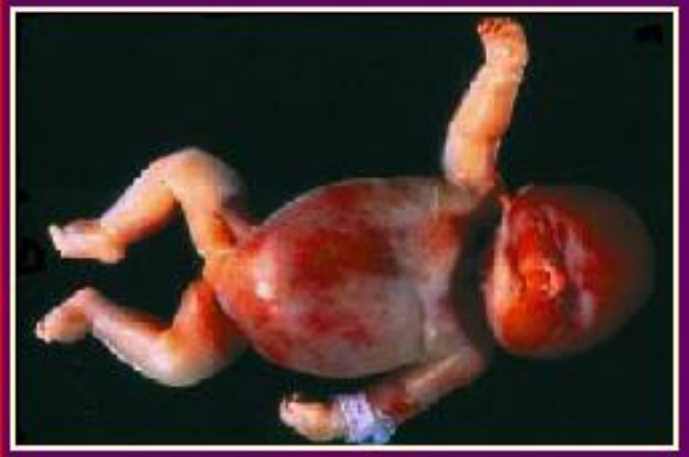


HPV B 19 & Erythema Infectiosum

- Human Parvovirus B-19 is most well-known for causing the childhood disease erythema infectiosum, better known as Fifth Disease

Table 1. Major Diseases Caused by Parvovirus B19.

Disease	Acute or Chronic	Host
Fifth disease	Acute	Normal children
Arthropathy	Acute or chronic	Normal adults
Transient aplastic crisis	Acute	Patients with increased erythropoiesis
Persistent anemia	Chronic	Immunodeficient and immunocompromised patients
Hydrops fetalis and congenital anemia	Acute or chronic	Fetus



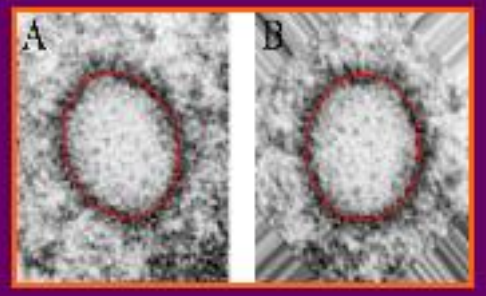
Hydrop fetalis

CMV

- **How is CMV spread?**
- Person to person contact (such as, kissing, sexual contact, and getting saliva or urine on your hands and then touching your eyes, or the inside of your nose or mouth)
- Through the breast milk of an infected woman who is breast feeding
- Infected pregnant women can pass the virus to their unborn babies
- Blood transfusions and organ transplantations

CMV

- Transmission of CMV occurs from person to person, through close contact with body fluids (urine, saliva (spit), breast milk, blood, tears, semen, and vaginal fluids), but the chance of getting CMV infection from casual contact is very small.



Some new potential Infections

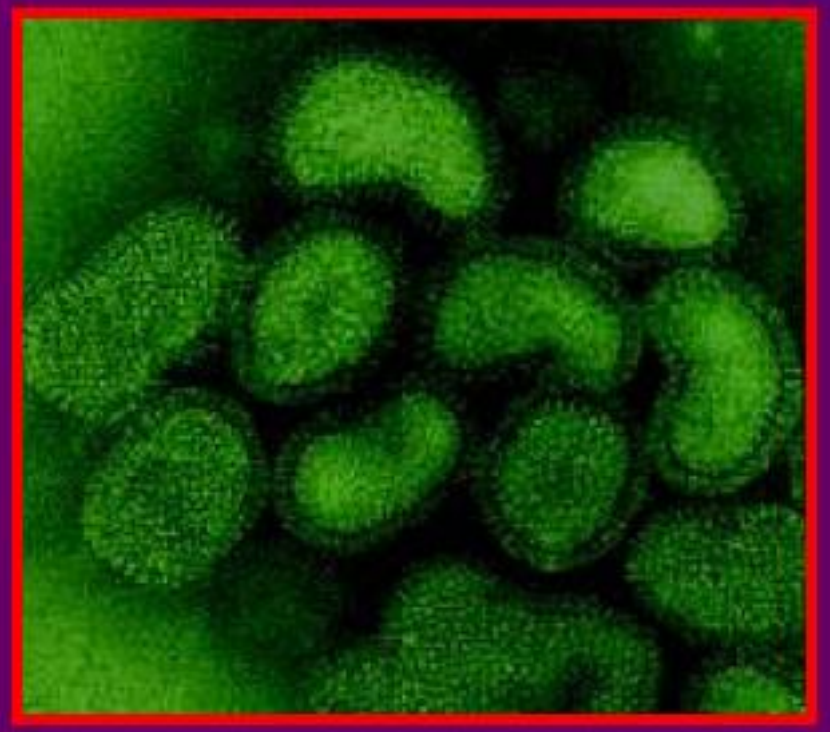
- ***Hemorrhagic fever viruses complex:***
  Ebola, Marburg, Bolibian HF, Argentinian HF, Hantaan virus etc.
- ***Encephalitis viruses complex:***

  West Nile Infections, Murray valley, Crimean-Congo encephalitic etc

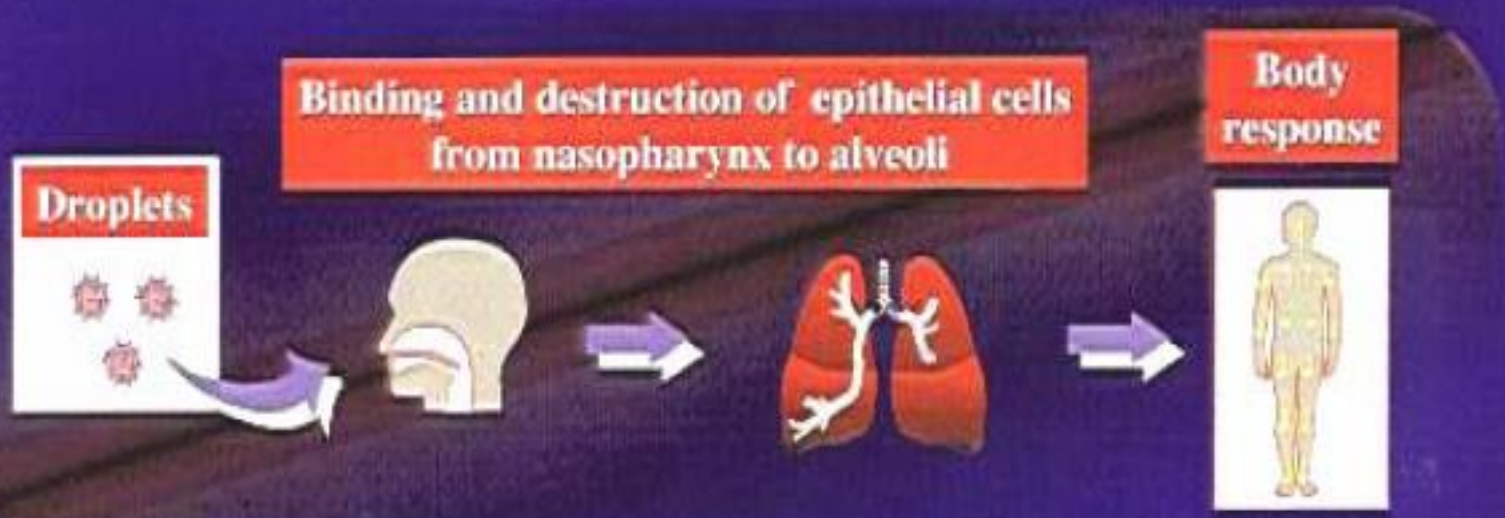
Could some important endemic infectious diseases create problem?

- Dengue virus infection
- Avian influenza
- SARS

Influenza & Avian Influenza Virus



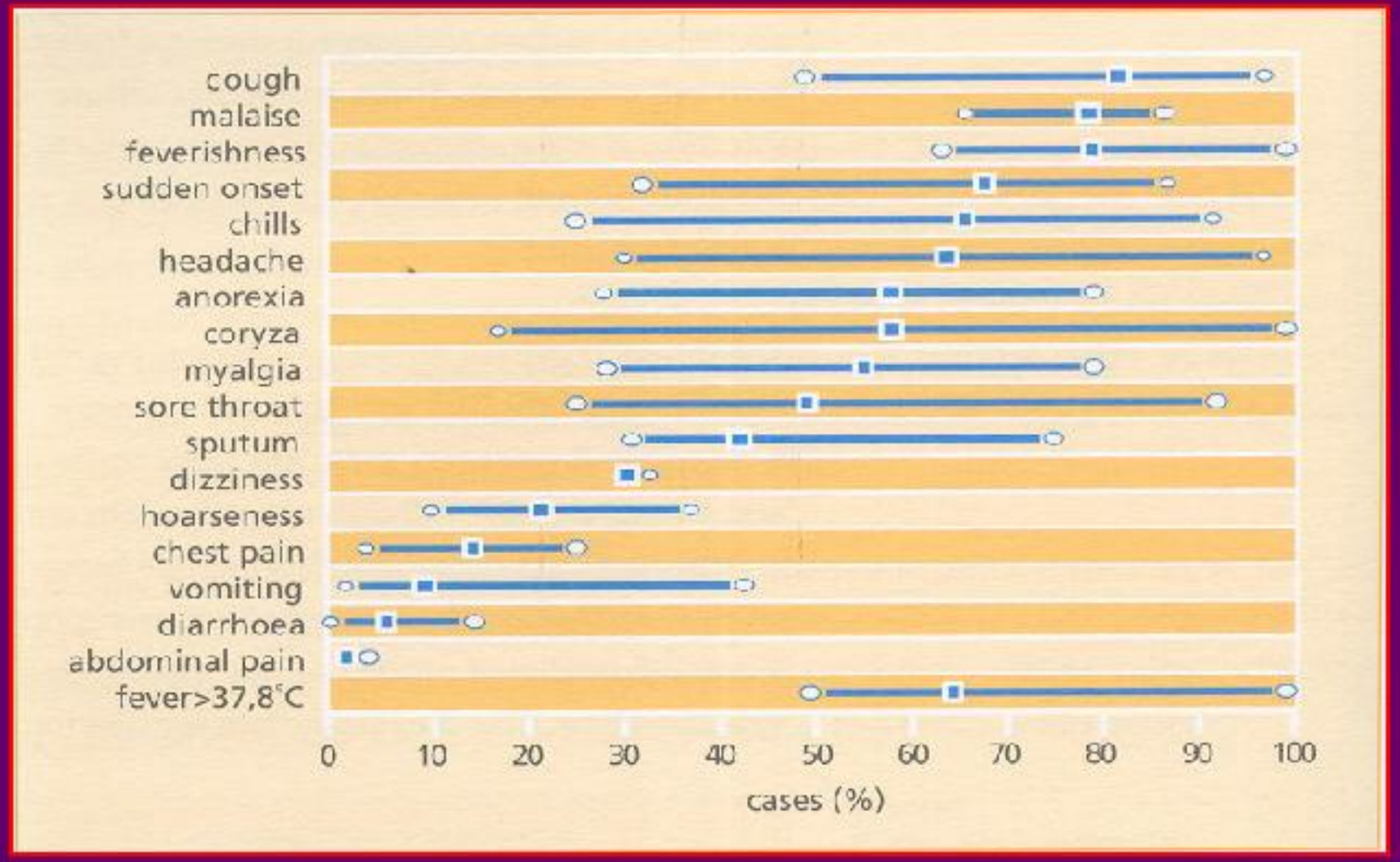
Physiopathology



LOCAL INFLAMMATORY REACTION
Upper Respiratory Infection

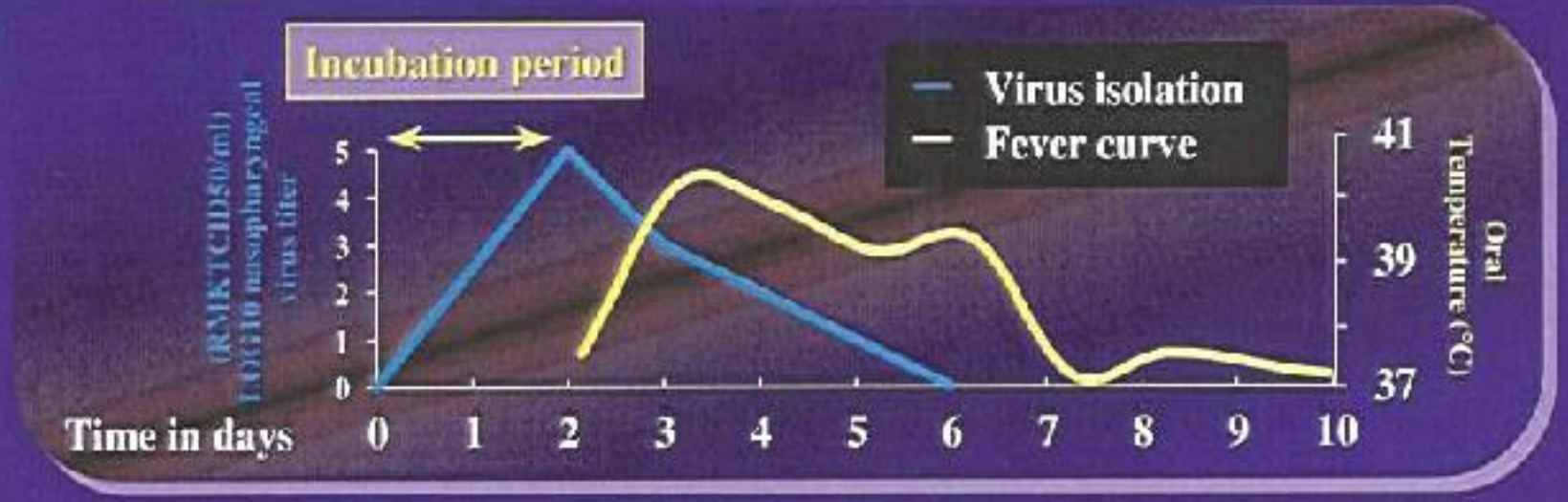
SYSTEMIC BODY REACTION
Fever, muscular pains...

Aymard M., Influenza : epidemiology, etiology, physiopathology, diagnosis, treatment, prevention, Vac 1993;47-70

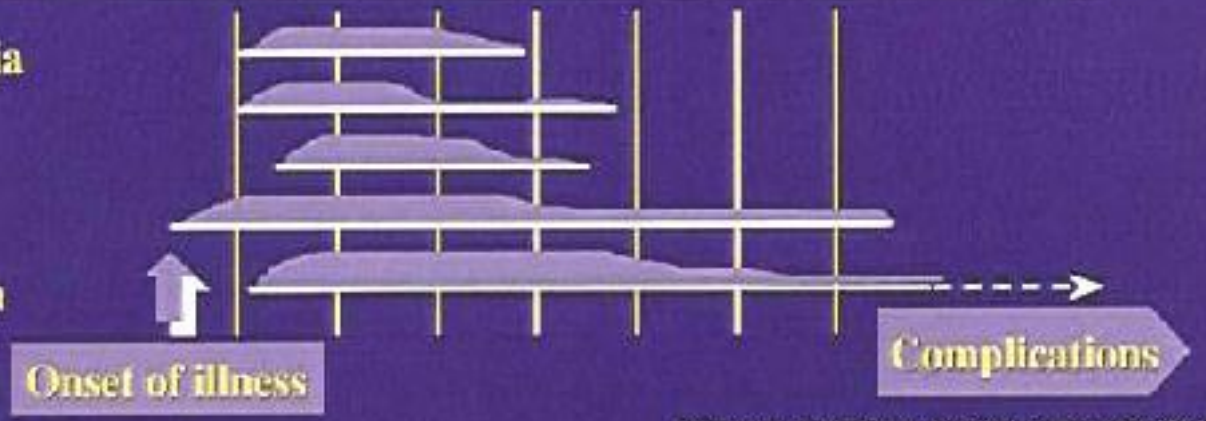


Influenza symptoms and their associated frequencies

The "traditional" flu



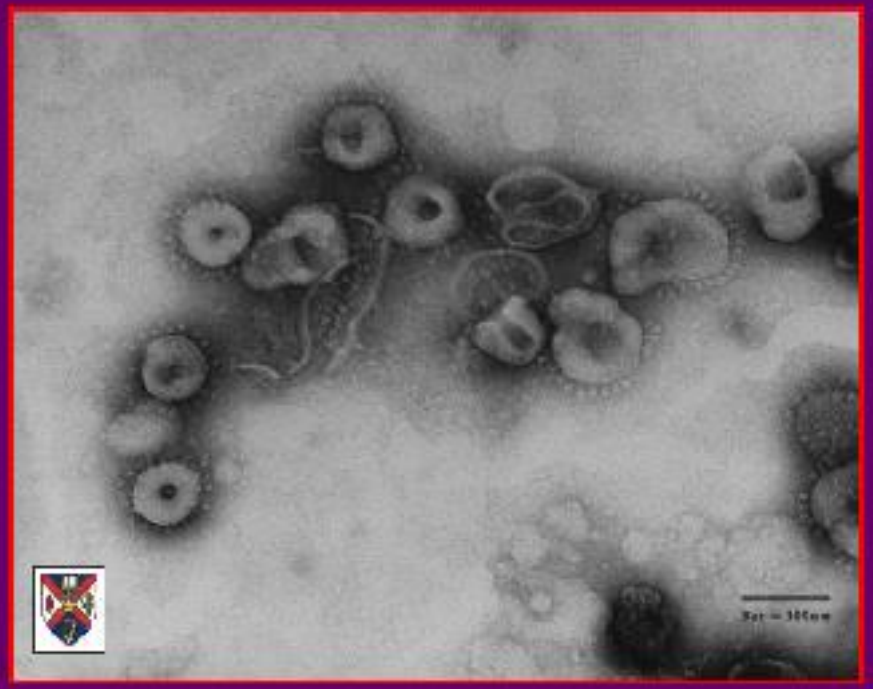
Sore throat, Myalgia
Headache
Cough
Coryza
Malaise, prostration



Kilbourne E. D., Influenza, New York, plenum 1987:156-218

Severe Acute Respiratory Syndrome (SARS)

SARS Corona Virus




موفق باشید