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Emerging Infections

presentation to East Midlands RTC meeting:

Threats, Disasters and Reducing Risk in Transfusion

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Caring Expert Quality

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What are emerging infections?

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Emerging infections

- newly recognised, although may not be new
- new infections, either new world-wide, or new to a particular area

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1969 “Infectious disease have been conquered”

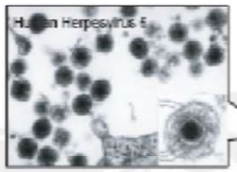
William Stewart, Surgeon General, USA

World Disaster Report 2000
International Federation of Red Cross/Red Crescent

INFECTIOUS DISEASE IS BIGGEST KILLER

13 million deaths in 1999
100,000deaths from natural disasters

Timeline of emerging infections since 1980



Hepatitis E virus
Human Herpesvirus 6

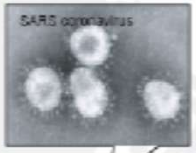
Sin Nombre virus
(Hantavirus pulmonary syndrome)

Human retroviruses,
HTLV3, HTLV4
Human Bocavirus

Escherichia coli O157:H7
HTLV2
Borrelia burgdorferi (Lyme disease)

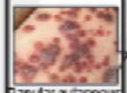
Guanarito virus
(Venezuelan
haemorrhagic fever)

Avian influenza A virus in humans
(H5N1)



Human T-lymphotropic
virus (HTLV-1)

Enterocytozoon bieneusi



Human Herpesvirus 8
(Kaposi Sarcoma virus)

SARS coronavirus

1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006

Pre 1980:
Monkeypox virus
Campylobacter jejuni
Cryptosporidium parvum
Legionnaire's disease
Ebola virus
Parvovirus B-19
Hantaan virus

HIV
Helicobacter pylori

Vibrio cholerae O139
Bartonella henselae

Sabia virus
Hendra virus

Nipah virus
West Nile virus in USA

Cyclospora cayetanensis
Bovine Spongiform Encephalopathy

Toxic Shock Syndrome associated
Staphylococcus aureus

Hepatitis C virus
Ehrlichia chafeensis
Photorhabdus asymbiotica

Simian foamy retroviruses

ncVJD
Bat lyssaviruses (Australia, UK)

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And since 2006.....

- chikungunya: Reunion (2006), Caribbean (2013)
- H1N1
- dengue
- Zika: Yap (2007), Polynesia (2013/4), central and South America, specifically Brazil (2015)

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Why does it matter?

- emerging infections are generally viral infections, with mosquito as the vector
- potential for transfusion-transmission due to (short) period of viraemia prior to illness, or sub-clinical infection
- increasing problem with “global warming” and spread of mosquitoes to previously unaffected areas

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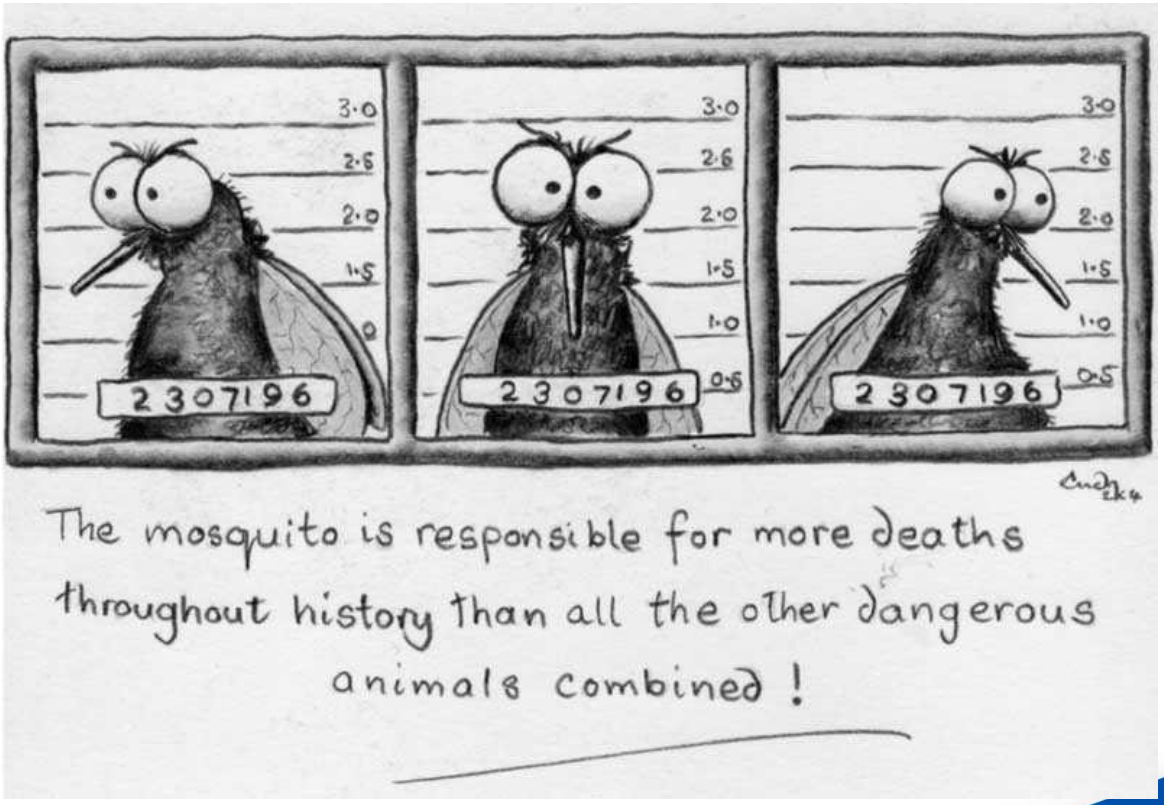
The villain of the piece!



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Basic questions relevant to blood safety

- is it a blood-borne agent?
- is it transmitted by blood/ tissues/ organs?
- prevalence of agent in donor population?
- could it be asymptomatic?
- can people at risk be identified?
- what disease and outcome?
- does the agent survive processing/ storage?
- are there tests? is testing warranted?

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HIV

- was an emerging infection once!

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Basic questions relevant to blood safety and AIDS 1982

- is it caused by a blood-borne agent? not clear
- prevalence of agent in donor population? not known
- could it be asymptomatic? yes
- can people at risk be identified? yes
- does the agent survive processing/ storage? not known
- is it transmitted by blood/ tissues/ organs? December 1982 evidence
- what disease and outcome? AIDS, fatal
- are there tests? is testing warranted? 1984 onwards

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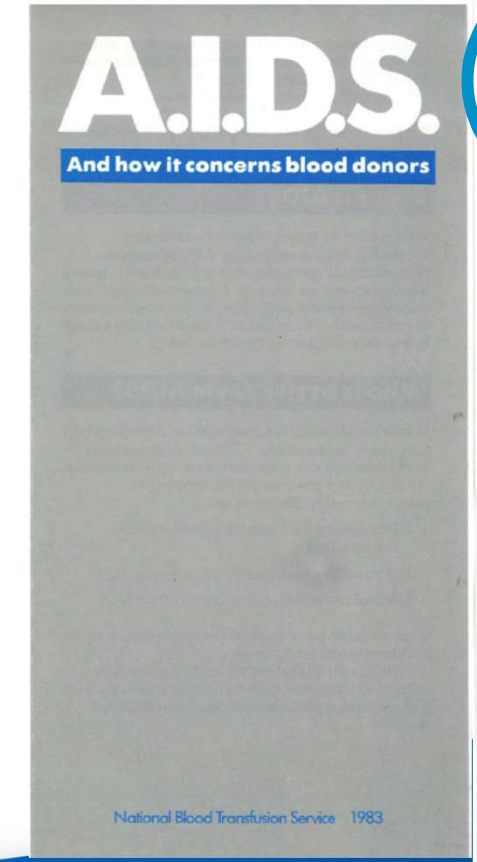
HIV, AIDS and MSM

- 1981 first cases described in young men
- December 1982 risk from transfusion identified
- Autumn 1983 DH leaflet ‘given’ to all donors



Donor Health Check for new and returning donors

Please answer the following questions in blue or black ballpoint pen. If you are uncertain of any answer, leave the box blank and speak in confidence to the nurse. Please do not use correction fluid if you make a mistake on this form.

A Your lifestyle	Yes	No	Staff
A1 Have you tested positive for HIV or do you think you may be HIV positive?			
A2 Have you ever had hepatitis B or hepatitis C or think you may have hepatitis now?			
A3 Have you ever injected yourself or been injected with illegal or non-prescribed drugs including body-building drugs or cosmetics (even if this was only once or a long time ago)?			
A4 Have you ever been given money or drugs for sex?			
A5 **In the last 12 months have you had sex with:**			
a anyone who is HIV positive;			
b anyone with hepatitis B, hepatitis C or HTLV;			
c anyone who has ever been given money or drugs for sex;			
d anyone who has ever injected drugs; or			
e anyone who may ever have had sex in parts of the world where AIDS/HIV is very common (this includes most countries in Africa)?			
A6 **Male donors only;** In the last 12 months have you had oral or anal sex with a man, with or without a condom?			
A7 **Female donors only;** In the last 12 months have you had sex with a man who has ever had oral or anal sex with another man, with or without a condom?			

B Your health	Yes	No	Staff
B1 Have you ever been told that you should not give blood?			
B2 Have you ever had a serious illness or seen a doctor about your heart?			
B3 Have you ever had any hospital investigations or tests or operations?			
B4 Are you taking any prescribed medicine or tablets or other treatments (except HRT for the menopause, the pill or other birth control)?			
B5 **In the last 7 days** have you taken any **additional** medicines or tablets including any you have bought yourself?			
B6 **In the last 7 days** have you seen a doctor, dentist or any other healthcare professional or are you waiting to see one (except for routine screening appointments)?			

C Risks of infection	DT CODE	Yes	No	Staff
C1 **In the last 2 weeks** have you had any illness, infection or fever or do you think you have one now?				
C2 **In the last 4 weeks** have you been in contact with anyone with an infectious disease?				
C3 **In the last 8 weeks** have you had any immunisations, vaccinations or jabs?				
In the last 12 months...				
C4 ...have you had your ears, face or body pierced, had a tattoo or any cosmetic treatment that involved piercing your skin?	S			
C5 ...have you had acupuncture?	S			
C6 ...have you been exposed **unintentionally** to someone else's blood or body fluids eg through a needle prick or bite or broken skin?	S			
Additional risks				
C7 Have you ever had jaundice or hepatitis?	J			
C8 Have you received a blood transfusion since 1st January 1980?				
C9 Has anyone in your family had CJD?				
C10 Were you treated with growth hormone before 1985?				
C11 Did you have brain surgery or an operation for a tumour or cyst in your spine before August 1992?				
C12 **Female donors only;** Have you ever had treatment for infertility?				

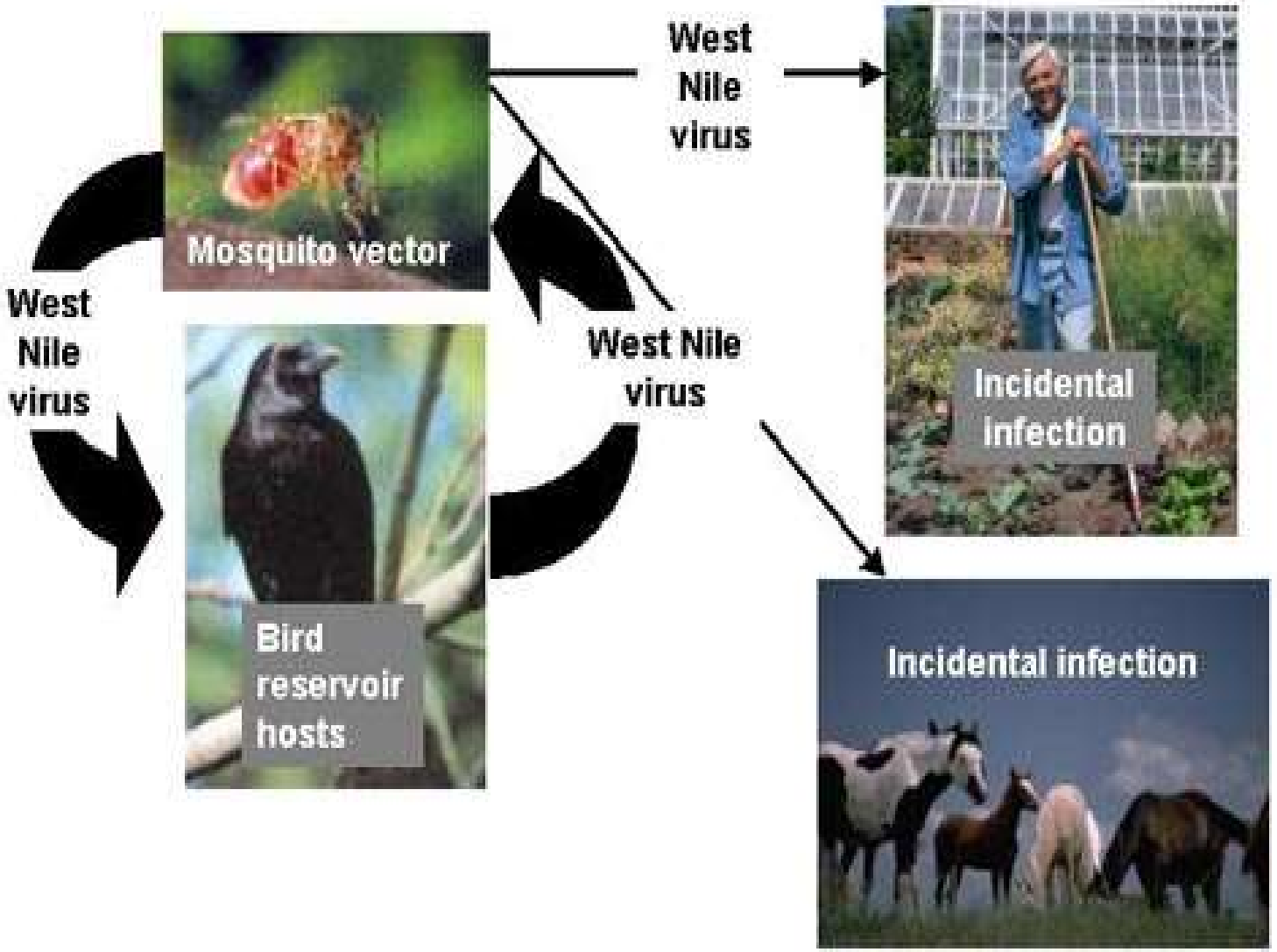
D Travel outside the UK	DT CODE	Yes	No	Staff
D1 **In the last 12 months** have you been outside the UK (inc. business trips)?	R			
D2a. Were you born or have you ever lived or stayed outside the UK for a continuous period of 6 months or more?	L			
b. If 'yes' have you been outside the UK since then?	L			
D3a. Have you ever had malaria or an unexplained fever which you could have picked up while travelling?	M/F			
b. If 'yes' have you been outside the UK since then?	V			
D4 Have you ever visited Central America or South America for a continuous period of 4 weeks or more?	R			
D5 Were you or your mother born in Central America or South America?	L			

(IN CAPITALS) Forename..... (IN CAPITALS) Surname.....

Your Signature..... Date.....

STAFF USE ONLY	CLINICAL NOTES
	☐ Suspend until...../...../.....
	☐ Withdraw
	☐ Accept

West Nile Virus Transmission Cycle



West Nile Virus

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- Flavivirus, first isolated in 1937 from West Nile district of Uganda
- pathogen of birds, incidental infections in horses and humans
  - transmitted by *Culex* and *Aedes* mosquitoes
  - often asymptomatic in humans
  - days to weeks later some develop flu-like symptoms
  - can result in WN encephalitis and/or death
- no specific drug treatment

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West Nile Virus (WNV)

- not a new infection: present in the “old world” for many years, recognised in horses/ birds/ humans
- “emerged” in North America in the 1990s
- caused widespread human disease with morbidity and mortality
- shown to be transmitted by blood transfusion and organ transplantation

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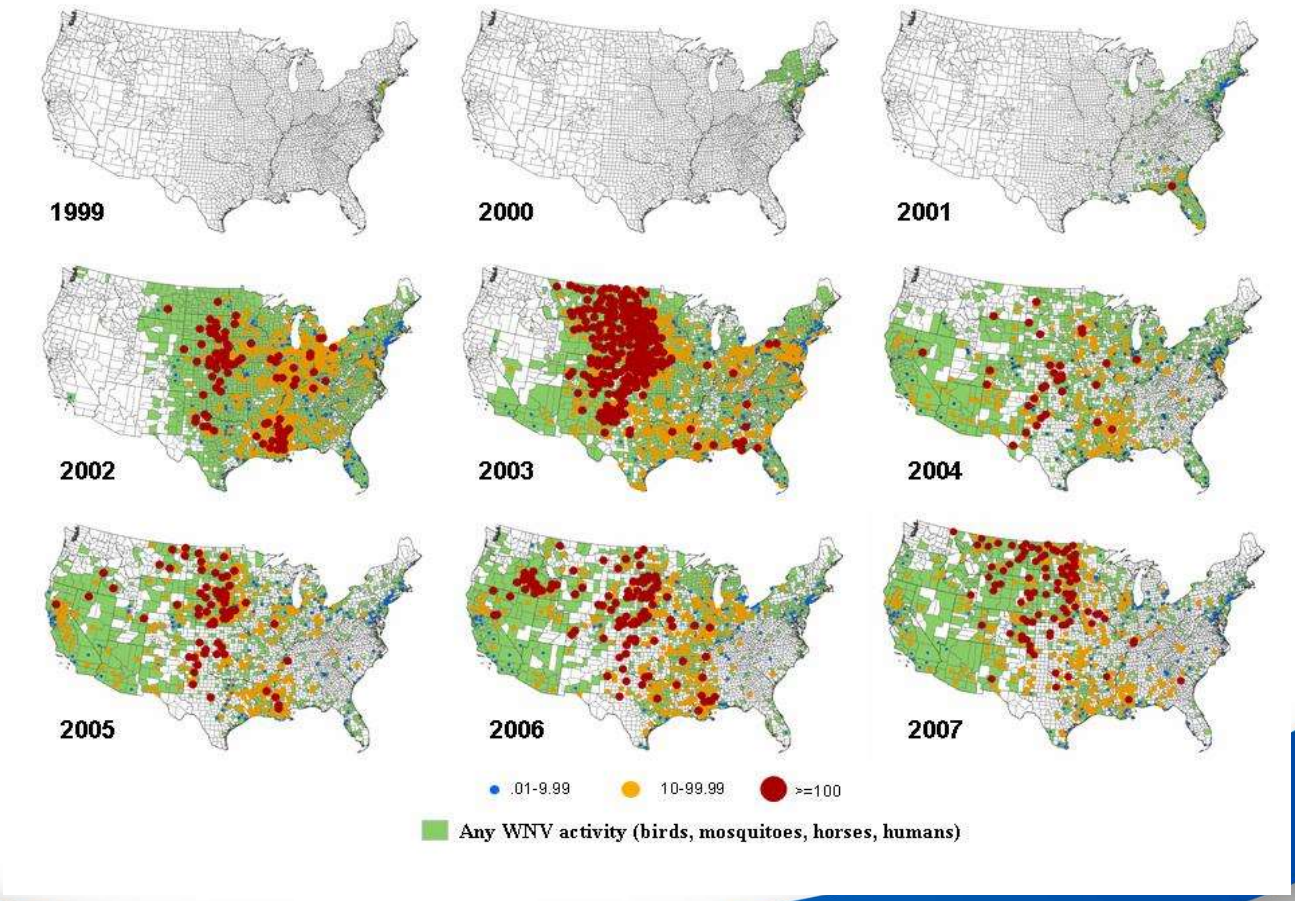
WNV in United States 1999- 2007



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West Nile Virus in north America

- epidemic spread across north America during mosquito season starting 1999
- transfusion-transmitted cases in 2002, also transplantation
- introduction of WNV NAT screening of blood donations: pools → individual tests

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WNV in north America

- UK introduced donor deferral, then WNV NAT testing for returning travellers
- samples referred to US and tested there
- impact on short shelf-life components
- 0 of >20,000 positive in 3 years testing in NHSBT; no imported cases in UK
- testing abandoned: donation loss tolerable

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West Nile Virus in Europe

- sporadic cases and outbreaks in humans and horses since the 1960s
- outbreaks in Romania (1996), Russia (1999), Israel (2000)
- sporadic cases in France (2003), Algarve (2004)

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Further developments

- 2009: spread in northern Italy; WNV NAT testing begins for blood donors in affected area.
- 2010: outbreak in northern Greece (against background of low level endemic activity): decision to implement WNV NAT testing.
- EU Directive: defer donors for 28 days after visit to area with “ongoing activity”

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UK response

- implement donor deferral for areas where WNV NAT testing of donations is in place
- consistent with other affected areas
- not necessarily consistent with other European blood services

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Will we have any blood donors left?

- 28 day deferral for visits to USA/ Canada, northern Italy
- more 28 day deferrals to follow
- will it be a blanket deferral for all travel outside UK?
- NHSBT travel survey: deferral for travel to Spain/ France would have huge impact

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Pre-2012 Olympics Planning

- potential donor loss if new areas affected
- may lead to blood shortages
- donor deferral may not be sustainable
- application to regulators: to use NAT testing
- NAT screening used since then: within NHSBT approx 38,000 donations tested/ year

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XMRV
or
the emerging infection that never was

- Xenotrophic murine leukaemia related virus
- 2006: described in association with prostate cancer
- 2009: described in association with chronic fatigue syndrome (CFS)

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What relevance to transfusion/transplantation?

- people with CFS already excluded as blood donors
- no evidence to suggest transmission
- no UK data on XMRV

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BUT

- pressure groups, lobbying, PQs, letters to CMO: aim to obtain funding for CFS research
- “premature” action in other blood services to seek previous history of CFS from donors
- late 2010/ early 2011 spent firefighting

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AND THEN

- findings not confirmed in any other laboratory: numerous scientific reports
- “positive” findings in original blood tests shown to be due to contamination

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XMRV

a submerged virus

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Zika virus

- first reported in Uganda 1947
- Flavivirus, transmitted to humans primarily through the bite of infected *Aedes* mosquito (*Ae. aegypti* and *Ae. albopictus),*
- mosquito vectors, aggressive daytime biters, feed indoors and outdoors
- non-human and human primates are likely main virus reservoirs, anthroponotic [human-vector-human] transmission occurs during outbreaks

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Zika virus

- emerged in Brazil 2015
- most infections asymptomatic or mild
- associated with neurological complications, microcephaly
- perinatal, sexual and transfusion transmission events have been reported.
- Zika RNA has been identified in asymptomatic blood donors during an on-going outbreak

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Zika virus: United States

- cases in Florida prompted FDA to instruct blood services to screen: throughout USA
- ID screening (not pools)
- short implementation period
- how/ when to stop???

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Action for Zika: UK

- Zika included on UK list of ‘tropical viruses’ for which donor deferral is in place
- travellers deferred for 28 days since last return from an affected area
- infected or symptomatic individuals deferred for 6/12
- sexual contacts.....

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And last but not least ....

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Prions

- vCJD emerged as a new human infection in 1995/6, transmitted from cattle (BSE)
- threat to blood supply proposed very early
- work started to assess the threat: is there a link between vCJD and blood transfusion?

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Transmission of prion diseases by blood transfusion

Hunter et al J Gen Vir 2002

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Articles

Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion

C A Llewelyn, P E Hewitt, R S G Knight, K Amar, S Cousens, J Mackenzie, R G Will

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vCJD risk reduction measures

- geographical donor deferral (not applicable in UK)
- leucodepletion (1998/9)
- importation of FFP for children and ? others
- importation of plasma for fractionated products
- exclusion of transfusion recipients as donors

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Transmission of vCJD by blood transfusion

- 4 infected recipients from 3 donors who later developed vCJD
- 3 recipients developed vCJD, 1 died before any clinical disease
- all transfused prior to 1999 with non-leucodepleted red cells

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vCJD :blood risk estimates

- tissue surveys suggest 1 in 2,000 of UK population are “infected”
- infections detected prior to 1980 and after 1996
- 177 of 178 clinical cases have been in genotype MM at codon 129 of PrP gene

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vCJD: Questions needing answers?

- will there be a second wave of vCJD in different genotypes?
- why have there not been more transfusion cases?
- has leucodepletion been more effective than predicted?

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When will we have the answers?

- surveillance will be needed for many years

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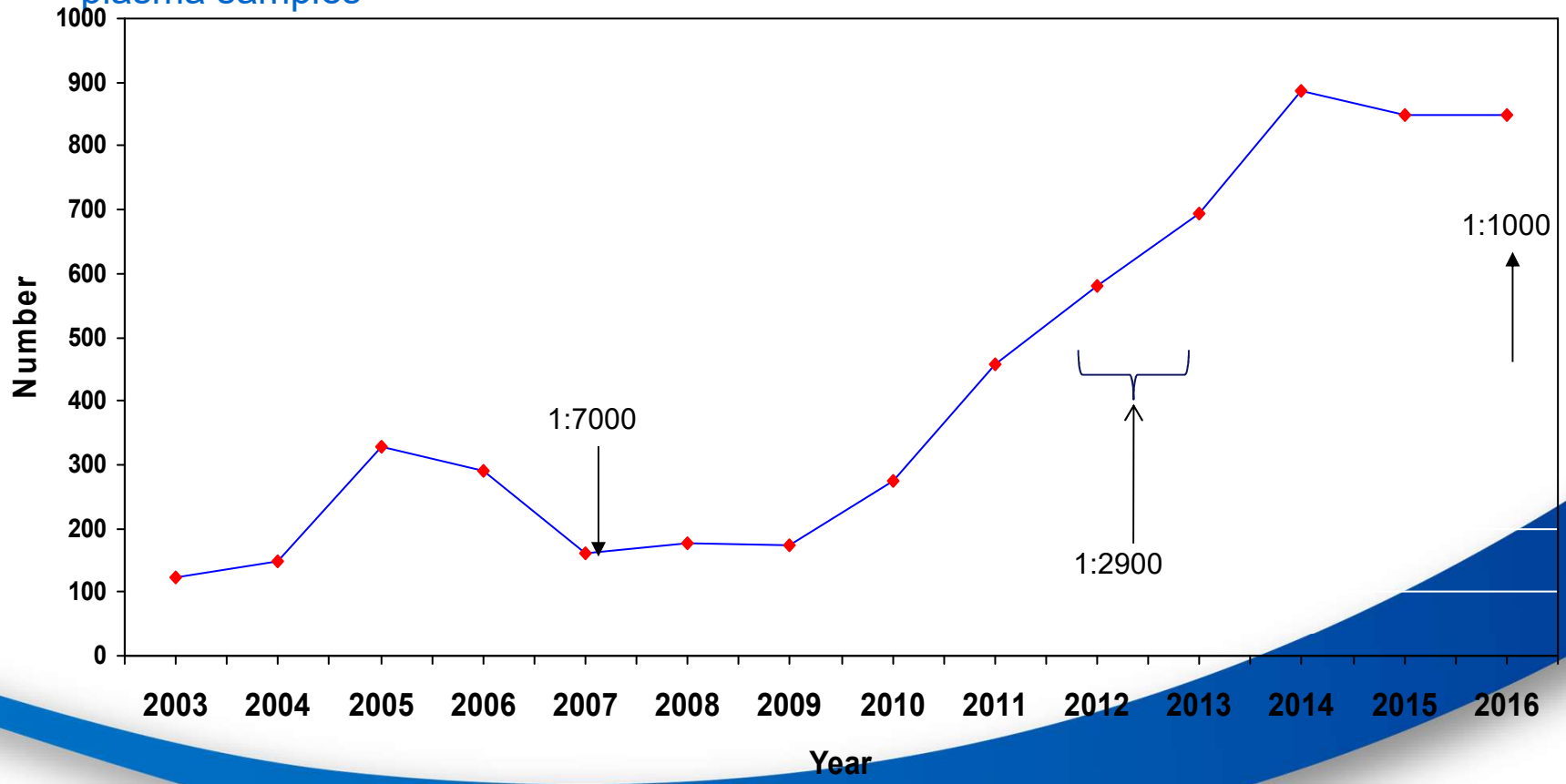
HEV

HEV infections in England and Wales 2003-2016:

graph: clinical cases reported to PHE

ratios: proportion of infected donations detected through NHSBT screening of pooled plasma samples



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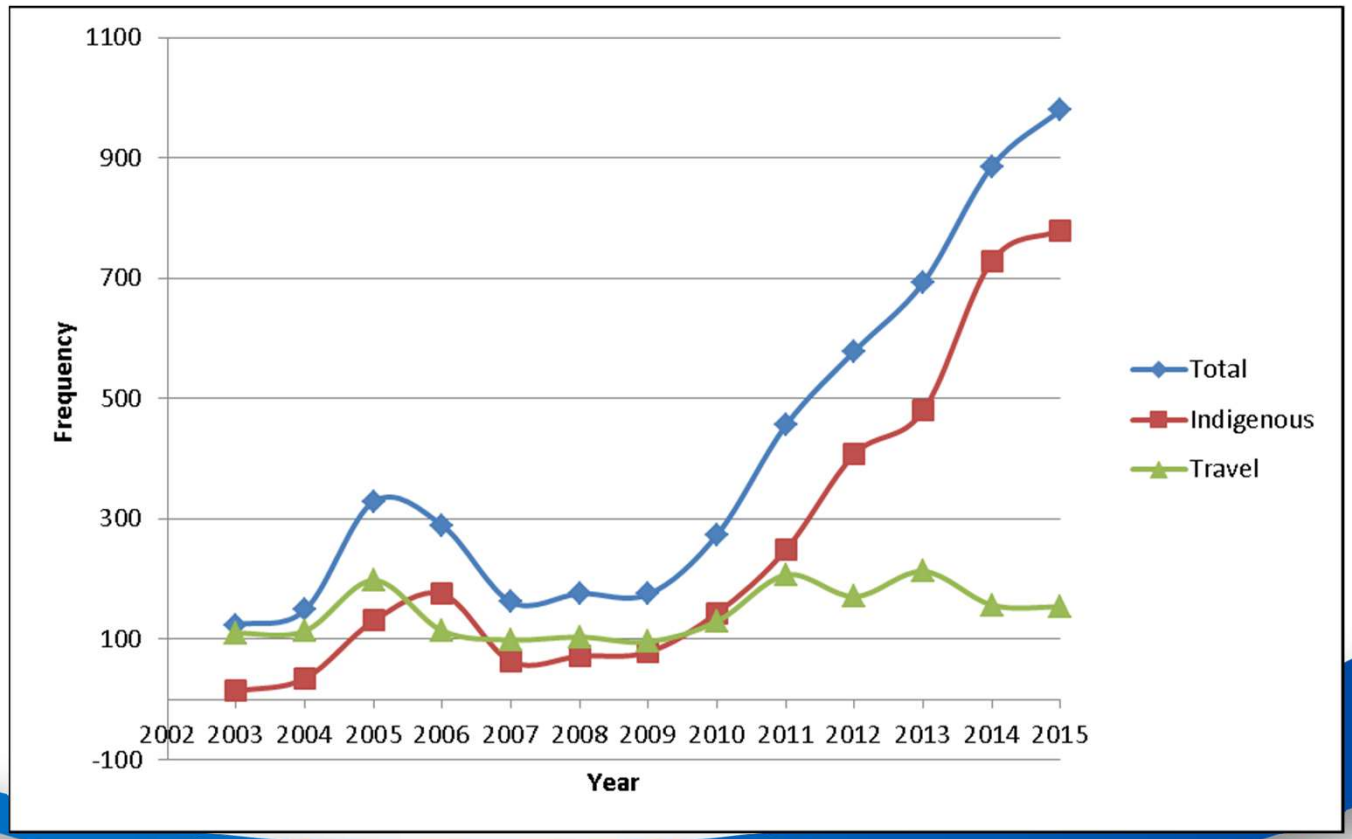
Public Health England

Why does this matter?

Imported versus indigenous infection in England/Wales



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HEV and blood safety?

- evidence of HEV turnover in blood donors in Europe
- post transfusion hepatitis linked to HEV reported from several countries including the UK
- reports of chronic HEV infections associated with immunosuppression
- high proportion of blood components given as haematological support to the immunosuppressed population

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Joint NHSBT-PHE study: HEV and Blood Safety

- retrospectively screen donors for HEV RNA to determine incidence of HEV infection in blood donors
- perform lookback to identify recipients of HEV RNA positive blood components and establish the outcome of receiving HEV-containing blood/blood components

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Incidence of HEV infection in blood donors

- 9382 minipools tested (x24) = 225,168 individual donations
- 78 HEV RNA repeat reactive (positive) donations

= 0.03% of donations HEV RNA positive

= 1:2900 donations HEV RNA positive

Lookback on recipients

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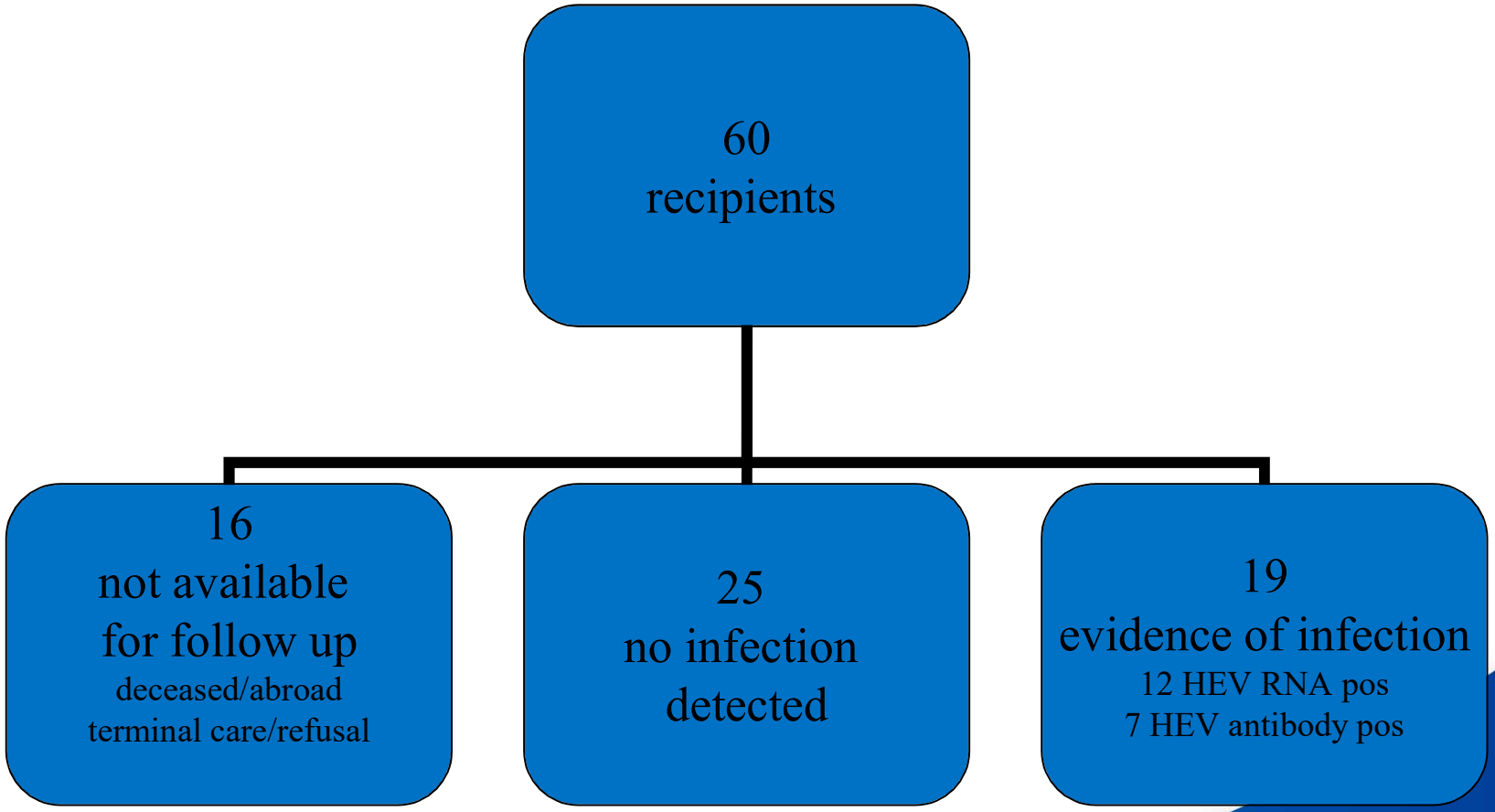

How did we get to where we are?

SaBTO: Professional advisory committee through Department of Health to Ministers (ToR). Working groups use a safety framework for any initiative:

a. Safety driven
b. Component supply initiative
c. Clinical driven initiative

} mitigation of HEV risk

2012/13 Donor transmission study [1]
1:2848 donors RNA +
42% transmission

SaBTO establish HEV working party 2013 – July 2015 accepted recommendations for HEV-testing of donors.*

final guidance for the use of HEV-negative blood components was approved by SaBTO on 13th January 2016

* Letter sent to HSCT/SOT physicians from SaBTO chair

[1] Hewitt *et al* Lancet 2014

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How did we get to where we are?

Public Health England

Issue of HEV RNA screened donations introduced in March 2016 in England *

SaBTO safety framework set an early review of HEV screening - HEV working party set up June 2016 ǂ

Final recommendations to be presented to SaBTO 1st November 2016

* NHS Blood and Transplant extended this recommendation to neonates <1 year of age

•ǂ Review: Direct costs faced by NBS, impact on mitigating hazard, component supply, linkages to other initiatives, external considerations, operational considerations, value for money.

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HEV 2017

- extended to universal screening of blood donations
- screening of organ, tissue and stem cell donors

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Conclusions

- emerging infections will continue to challenge us
- robust surveillance and risk assessment are paramount
- ? role of pathogen inactivation in the future

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- And especially Marcela Contreras and John Barbara