Blood Transfusion: How Safe is Safe?

The 15th Annual Bill T. Teague Lectureship in Transfusion Medicine

Celso Bianco, MD
Houston, TX
May 19, 2011
I was asked to address two questions:

1. Why did FDA and the blood bank community move to a zero-risk policy?

2. With the changes in healthcare and the state of the economy, do I see a future shift in this approach, starting with policies from FDA?
Cumulative U.S. AIDS Cases
as of 5/85  N~10,000

Each point = 30 cases
Cumulative U.S. AIDS Cases
as of 7/89  N~100,000

Each point = 30 cases
Cumulative U.S. AIDS Cases
as of 12/95  N~500,000

Each point = 30 cases
AIDS from blood

CDC: AIDS public use data file

N=9152
The Past Decade
2002 - 2003

- New vCJD deferrals, donor loss 5-10%
- Transmission of West Nile Virus by blood
- FDA Guidance on Smallpox Vaccination
- White Particulate Matter
- AABB Standard 5.1.5.1 “detect bacterial contamination in all platelet components”
- SARS (Severe Acute Respiratory Syndrome)
- Screening of recovered plasma for B19
- Alert about Monkeypox virus infections
- ASBPO deferral for travel to Iraq: Leishmania
West Nile Virus Activity
Cumulative results for 2000 calendar year
West Nile Virus Activity

Non-Human WNV Activity
Human Disease Cases

National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2003 calendar year reported as of May 20, 2004
West Nile Virus Activity

Cumulative results for 2005 calendar year reported as of February 14, 2006
The Past Decade
still in 2003

July – Aug 2003 Nationwide screening for WNV by NAT under IND is implemented
WNV in the US 1999-2010

Estimated no. of infections: between 1.9M (1:150) and 4.4M (1:350)
WNV Blood Screening in the U.S.

- From 2003 to 2010 resulted in:
  - Interdiction of >3,000 WNV NAT-reactive units
  - Prevention of 3,000 to 9,000 potential WNV transmissions by transfusion

### Transmission by Transfusion

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAT-Reactive Units &gt;1,000</td>
<td>&gt;1,000</td>
<td>224</td>
<td>417</td>
<td>441</td>
<td>511</td>
<td>235</td>
<td>222</td>
<td>~200</td>
</tr>
<tr>
<td>TT Confirmed* (n=32)</td>
<td>6 ‡</td>
<td>1 ‡</td>
<td>0</td>
<td>2 ‡</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TT Inconclusive+ (n=26)</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All seronegative for WNV; ‡ Lack of f/up, sample, recipient loss
‡ Negative in MP-NAT and positive on ID-NAT (low viremia)
The Past Decade
2004 - 2007

- Guidances for NAT for HIV and HCV
- More AABB Bulletins on bacterial detection
- AABB Bulletins on measures to reduce risk of TRALI (Transfusion-related Acute Lung Injury)
- More FDA Guidances for assessment of donor suitability and product safety in cases of WNV
- Guidance for appropriate screening for HBV (increased sensitivity requirements)
- Screening for antibodies to T. cruzi in most of the U.S. in February 2007
The Past Decade
2008-2011

- FDA collection of platelets by automated methods (statistical process control)
- AABB Bulletin on “triggering” ID-NAT for WNV
- Draft and final Guidances for screening for antibodies to Trypanosoma cruzi (Chagas)
- Guidances on management of donors positive on NAT for HIV, HCV and HBV
- Revised Guidance for prevention of vCJD transmission
- Guidance for “Lookback” for HCV
- Guidance for pre-storage leukoreduction, statistical methods included
FEAR!
FEAR of the unknown and the uncontrollable!
Two routes. Most visual input heads for the cortex (solid arrow), but some is shuttled subcortically (dotted arrow).

Science 300:568-9, 2003
Blood is safer than it has ever been, but...

- We still confront major challenges
- Expectation of zero risk by the public and recipient advocacy organizations
- The reaction of accreditation organizations and regulatory agencies to these expectations
- The Precautionary Principle
Risk Perception, Slovic et al., 1987

- Unknown risk
- Not observable
- Unknown to those exposed
- Effect delayed
- New risk
- Risk unknown to Science

- Known
- Observable
- Known to those exposed
- Effect immediate
- Old risk
- Known to Science
Risk Perception, Slovic et al., 1987

- Controllable
- No Dread
- Consequences Not Fatal
- Individual
- Low Risk to Future Generations
- Easily Reduced
- Risk Decreasing Voluntarily

- Uncontrollable
- Dread
- Fatal
- Catastrophic
- High Risk to Future Generations
- Not Easily Reduced
- Increasing Involuntarily
Perception of Risk

Unknown Risk

No Dread

Dread Risk

Known Risk

Perception of Risk

- Nuclear Reactor Accident
- Auto Racing
- Saccharin
- Home Swimming Pools

Perception of Transfusion Risk

No Dread

- HHV-8
- B19 Parvovirus
- Babesia
- HBV

Known Risk

- Chagas
- Dengue

Unknown Risk

- XMRV
- Ebola
- vCJD
- WNV
- HIV

Dread Risk

The Major Challenges

- Environmental/Social
- Expectation of zero risk
- The Precautionary Principle
The “Precautionary Principle”

“in order to protect the environment, the precautionary approach shall be widely applied by States according to their capability. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation”.

Declaration of Rio, 1992
Report of Mr. Justice Horace Krever, November 1997

...the decision of the Red Cross not to implement anti-HBc and ALT testing of blood donations in Canada as surrogates for non-A, non-B hepatitis was not an acceptable one....

The Canadian Response to Post-Transfusion Hepatitis, Krever Commission Report, p.707
“the safety of the blood supply is an aspect of public health, and, therefore, the blood supply system must be governed by the public health philosophy, which rejects the view that complete knowledge of a public health hazard is a prerequisite for action.”

Justice Krever, Canada, 1997
Variant CJD (vCJD)

“TSE” or prion disease (Transmissible Spongiform Encephalopathies)
Consumption of tissue from “Mad Cows”
Degenerative, fatal disease, long incubation
Most cases in UK (169), ~39 elsewhere
No endogenous cases in US
– 2 UK exposure, 1 Saudi Arabia
Risk appears to be declining but
  Unknown number of exposed individuals
  “Second wave” possible since genotypes other than met/met at codon 129 of PrP could have longer incubation periods (met/val, val/val)
<table>
<thead>
<tr>
<th>YEAR</th>
<th>POLICY</th>
<th>EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>vCJD discovered</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>Recall all derivatives from individuals later diagnosed vCJD</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>UK Import plasma for fractionation</td>
<td>UK, France then Canada universal leukoreduction</td>
</tr>
<tr>
<td>1999</td>
<td>US and Canada, UK deferrals</td>
<td>Preliminary report Sheep to sheep tx of vCJD by transfusion</td>
</tr>
<tr>
<td>2000</td>
<td>France, UK deferrals</td>
<td>Confirmed exp tx</td>
</tr>
<tr>
<td>2002</td>
<td>US, 3 mo UK, 5 y Europe deferrals</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>UK starts importing plasma for patients born after January 1996</td>
<td></td>
</tr>
</tbody>
</table>
vCJD diagnoses in the U.K. by year

http://www.cjd.ed.ac.uk
### vCJD in the World (March 2011)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>PRIMARY CASES (ALIVE)</th>
<th>RESIDENCE IN UK &gt; 6 MONTHS 1980-1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>172 †(4)</td>
<td>175</td>
</tr>
<tr>
<td>France</td>
<td>25 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Republic of Ireland</td>
<td>4 (0)</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>2 (0)</td>
<td>0</td>
</tr>
<tr>
<td>USA</td>
<td>3† †(0)</td>
<td>2</td>
</tr>
<tr>
<td>Canada</td>
<td>2*(1)</td>
<td>1</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Japan</td>
<td>1**(0)</td>
<td>0</td>
</tr>
<tr>
<td>Netherlands</td>
<td>3 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Portugal</td>
<td>2 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>5 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1 (0)</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>221</strong></td>
<td></td>
</tr>
</tbody>
</table>

†U.K. cases associated with blood transfusion 3
†† 3rd US case born and raised in Saudi Arabia
** Japan case resided in the UK for 24 days 1980-1996
Impact of vCJD Deferrals

- Big issues: confusion and self deferrals
  - ARC ~ 600,000
  - ABC ~ 300,000
  - Euroblood (NYBC) ~140,000
  - Military (25%) ~ 30,000
- Total loss in 2002 ~ 1.1 million donors, 1.7 million units;
- Additive, still growing

The smallest human epidemic ever recorded in medical history
Other vCJD interventions in the US?

- Prion filtration
  - Impact on quality of product
  - Need in the face of no autochthonous cases
  - Cost
- Prion testing
  - Current assays incompatible with operations
  - Performance, confirmation and predictive value in the face of immeasurable incidence
  - Cost
  - Utility to recover deferred donors
Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome

Vincent C. Lombardi,1* Francis W. Ruscetti,2* Jaydip Das Gupta,3 Max A. Pfost,1 Kathryn S. Hagen,1 Daniel L. Peterson,1 Sandra K. Ruscetti,4 Rachel K. Bagni,5 Cari Petrow-Sadowski,6 Bert Gold,2 Michael Dean,2 Robert H. Silverman,3 Judy A. Mikovits1†

Conclusions re: CFS and XMRV

- XMRV found in 67% of CFS patients
- An immune response to the virus was detected in some CFS patients
- Data suggest that the human population is at risk from infection with XMRV (3.7% of controls DNA positive)

“Given that infectious virus is present in plasma and in blood cells blood-borne transmission is a possibility.”

XMRV: future (blood) scenarios

Unknown & unpredictable
- Irrelevant
- TTV/SEN
- GBV-C
- SFV (unless you live in Canada)

Doomsday
- Dread disease with long incubation
- Transmission documented
- Already widespread
- Viral drift increasing pathogenicity
Options to react to XMRV

- Do nothing while sorting out the science
- Interim intervention
  - Donor testing:
    - none available, commercial potential unclear, no confirmed disease associations, unknown impact on supply
  - Donor history deferral:
    - CFS (and CaP) are surrogates of little predictive value if 4-7% of the population is infected (but very low “cost”)
XMRV: current status

- Controversial literature with no causality established in prostate cancer or CFS
- Transfusion transmission plausible
- No gold standard test
- No other predictive intervention available
- High concern when HIV is the model
- High interest from “affinity groups”
- CBS, Australia, UK, NZ with passive deferrals
“...AABB recommends that blood collecting organizations make educational information available regarding the reasons why an individual diagnosed with CFS should not donate blood...."
Key issues for blood community

- Confirm or refute associations with CaP & CFS using validated assays
- Causal
- Confounder
- Contamination
- Establish transmission route(s)
- Tissue/cell tropism in humans
- Involvement in other human diseases
- Interim approach to blood donation
XMRV SRWG - Study Phases

- **Phase I - Analytical Panels**
  - Evaluate performance of XMRV NAT assays

- **Phase II - Pilot Clinical Studies**
  - Whole Blood versus PBMC
  - Timing of sample preparation

- **Phase III - Clinical Sensitivity/Specificity Panel**
  - Assay performance on pedigreed clinical samples

- **Phase IV - Blood Donor Clinical Panel**
  - Initial estimation of XMRV nucleic acid prevalence in blood donors
  - Initiation of donor seroprevalence studies
Other Unresolved and Partially Resolved Blood Safety Issues

- Babesia
- Dengue
- Bacterial detection
- TRALI
- Blood Utilization
- Errors
- …
Our largest risks aren’t emerging infections

- HIV
- HCV
- HBV
- Bacteria
- Mistransfusion
- Lung injury
- GVHD
- Cardiac
- Metabolic risk in neonates
- Under transfusion

Death in hospital from medical error (IOM, 1999)

After S. Dzik, MD Blood Transfusion Service, MGH, Boston

Cardiac

Metabolic risk in neonates

Under transfusion

Death in hospital from medical error (IOM, 1999)
Experts identified arboviruses that already are, or have the potential to spread in the US because hosts and vectors are here:

- **St. Louis Encephalitis and La Crosse** are endemic in the US; others are of current and future concern are:
  - **Dengue**: 10,000 cases/year in Puerto Rico, recent mini-epidemic in Key West, FL
  - **Chikungunya**: explosive epidemics in the Indian Ocean and recent mini-epidemic in Italy
  - **Japanese Encephalitis** in India (vaccine available)
  - **Yellow Fever** in South America (vaccine available)
FDA Workshop: Emerging Arboviruses

Donor Screening Assay Manufacturers

- **Novartis/Gen-Probe (ex-Chiron)**
  - Provided dengue TMA kits for donor prevalence studies in Puerto Rico, Honduras and Brazil
  - *At present sees no commercial viability due to lack of regulatory framework, competing priorities*

- **Roche**
  - Research multiplex PCR for dengue and Chikungunya under development
  - *No plans for prospective studies in donated blood*

- **NS1 Ag EIA for dengue (Bio-Rad)**
  - 82-83% sensitivity in published studies relative to PCR
  - ARC is using the assay under IND in Puerto Rico
Transfusion Medicine Community Concerns

🔥 In the Old Times, developers took risks
They invested in discovery programs before knowing what the outcomes would be (Abbott Hepatitis Discovery Programs, Chiron’s search for the non-A, non-B hepatitis virus)
🔥 They competed for leadership and primacy
🔥 Today, manufacturers of diagnostics shy away from donor screening and choose not to submit assays available in other countries for US clearance
Limited Financial Resources Applied to Blood Collection/Transfusion

- Blood collection/transfusion is a mature industry
- 17 million WB collections, 6% increase between 2006 and 2008 (AABB/DHHS Survey)
- ~2 million apheresis platelets, ↑16% 2006 to 2008
- Limited prospect for further growth
- Unknown impact of blood management, biovigilance, etc.
- Utilization and blood management consultants promising substantial reduction in costs
- Practice Guidelines in US, Canada, UK

Manufacturers
- Less than 1% of revenue of J&J, Abbott, Gen-Probe/Novartis, Roche comes from blood
- Profit margins for blood screening are way below those of pharmaceuticals
WW Donor Screening Market - 2007

Donor Screening

~ $1.4B or 4%

Serology  NAT

WW IVD

~ $34B

2007

www.AmericasBlood.org ★ 1-888-USBLOOD
WW IVD Market Growth

2007

~$32B

Other 4%

DS 4%

2013

~$60B

DS 3%

Source: BBC 2007
Business Challenges

- Oversupply, competition
- High demand for investment in infrastructure, informatics, new tests and quality systems
- Shrinking donor base because of regulatory mandates, aging and travel
- In the black, but in general cash poor
- Limited investment in infrastructure/new business
Needed Changes

- How can Transfusion Medicine become financially more attractive for product manufacturers in the current environment?
- How can we overcome the inhibitory effect of the recent US history of regulatory failures?
- Oxygen carriers
- Pathogen Inactivation
- How can we find alternative pathways for approval / licensure of assays with a limited market (e.g. confirmatory assays, HTLV-I/II, confirmation for HIV-2, malaria, babesia)?
Needed Changes

- How can we deal with public concerns about blood? Can we educate patient advocacy groups and consumers? Should we emphasize the benefits of transfusion; some risk is unavoidable but many of us are alive because of them.

- The search for additional safety measures does not mean that blood is unsafe!

- How can we encourage and actively support the development of evidence based policies, as opposed to rigid precautionism that does not tolerate potential risks and inhibits innovation.
BEYOND THE PRECAUTIONARY PRINCIPLE
Cass R. Sunstein
THE LAW SCHOOL THE UNIVERSITY OF CHICAGO
January 2003

This paper can be downloaded without charge at:
The Chicago Working Paper Series Index:
http://www.law.uchicago.edu/Lawecon/index.html
and at the Social Science Research Network
Electronic Paper Collection:
http://ssrn.com/abstract_id=307098
Sunstein on the Precautionary Principle

“In its strongest and most distinctive forms ... it requires regulation of activities even if it cannot be shown that those activities are likely to produce significant harms.”

“The principle is literally paralyzing—forbidding inaction, stringent regulation, and everything in between.”

“It should be rejected, not because it leads in bad directions, but because it leads in no directions at all.”
International Consensus Conference on

Risk-Based Decision Making for BLOOD SAFETY

OCTOBER 26 TO 28 2010
TORONTO CANADA
at The Westin Harbour Castle

DRAFT REPORT by the CONSENSUS PANEL
October 28, 2010

Canadian Blood Services
AAAB
American's Blood Centers
American Red Cross
Australian Red Cross Blood Service
Blood Systems, Inc
European Blood Alliance
Häme-Guille
National Health Service Blood & Transplant (UK)
Consensus: Possible Solutions

1) A comprehensive approach to blood safety requires the development of an integrated risk management framework that encompasses “vein to vein”, and beyond.

2) Decision making based on transparent principles of risk management.

3) A system that balances risks, costs, and benefits in a sustainable manner.

4) Meaningful engagement with interested and affected parties throughout the process of risk decision making.

5) Adherence to well-established ethical principles, including autonomy, beneficence, nonmaleficence, and justice to ensure that the rights of both donors and patients are respected.
In making these recommendations, the panel makes the following assumptions:

A. The precautionary principle suggests that, in the interests of public health, risk management action should be taken in the absence of certainty about risk.

B. The goal of proactive risk management is to anticipate, prevent, and mitigate risk to extent possible.

C. The principle of risk based decision making suggests that risk management actions should be proportionate with the level of demonstrated risk.
The ultimate question

2. With the changes in healthcare and the state of the economy, do I see a future shift in this approach, starting with policies from FDA? In my opinion, yes, there will be a shift

The evolving social and economic environment will drive changes

Public perception will be the last to change... based on evidence, education and on availability of care

FDA will change after public perception changes

Unfortunately, it will take a while; only the very young among us will see the changes
“The future ain’t what it used to be …”

Yogi Berra
Special thanks to Maria Rios, PhD
and Louis Katz, MD for some of the materials presented

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