US perspective/experience on modeling studies for donor deferral

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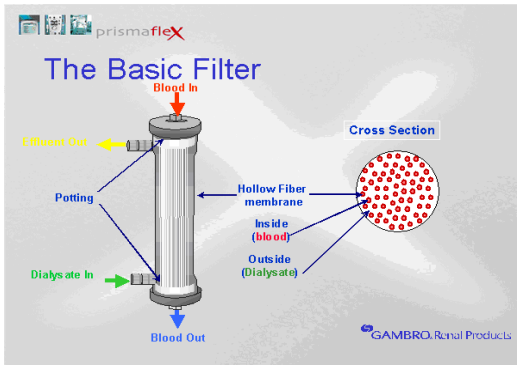
Risk Mitigation for TTID

Donor questionnaire

Blood testing



Pathogen reduction

Donor Deferral

- The first line of protection
- Donor loss
- Operational burden
- Benefit-risk approach to evaluate donor deferral options

Modelling TTID Risk & Evaluation of Policy Options

Risk behavior
Travel exposure

Donor risk

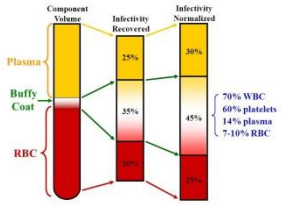
Risk mitigation/Regulatory options

Donor deferral

Blood testing

Pathogen reduction

Distribution of infectivity in blood components



Infectious units

Infectivity

Product usage

Dose response

Recipient risk

Why Modeling?

- To integrate a complex system for benefit-risk assessment
- Incorporate data uncertainty
- Evaluate risk factors and risk attribution explicitly
- Outline model components and assumptions
- Facilitate discussion and improve communication

FDA Risk Assessment for Variant Creutzfeldt-Jakob Disease (vCJD)

- vCJD risk via US plasma-derived factor VIII (FVIII), 2003-2009
- vCJD risk via US red blood cells (RBC), 2009-2013
- Geographic vCJD risk and donor deferral options, 2013-2016

Variant Creutzfeldt-Jakob Disease

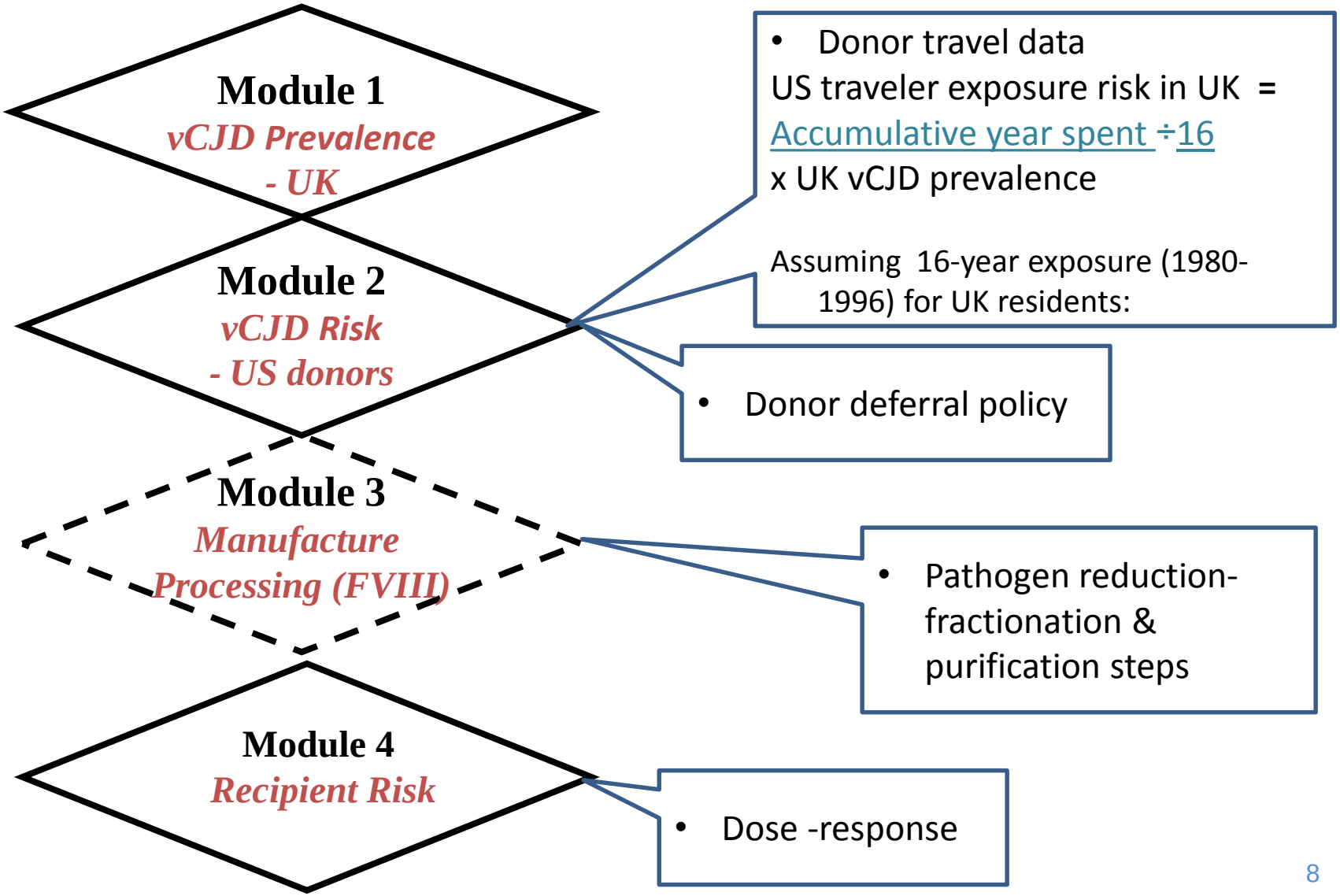
- Fatal neurodegenerative disease in humans
  - 230 cases worldwide since 1995, 178 cases in UK
- Acquired through consumption of beef from cattle infected with Bovine Spongiform Encephalopathy
- Transmitted through human blood and plasma products
  - 4 cases transmitted through blood transfusion
  - 1 case transmitted through blood clotting factor
- Long incubation period (15 years or longer)
- No FDA approved blood screening test
- Infectivity in blood can't be eliminated, but may be partially removed through plasma fractionation and purification

FDA Guidance for Donor Deferral

Indefinitely defers donors having history of accumulated time spent in:

- UK ≥ 3 months, 1980-1996
- Other countries in Europe ≥ 5years 1980-present (not include source plasma donors)
- US military base ≥ 6 months, 1980-1990 in N. of Alps or 1980-1996 in S. of Alps
- Having received transfusion in UK, France

Case Studies: vCJD Risk Assessment for RBC & Plasma Derived Factor VIII



Major Model Uncertainty
- UK vCJD Prevalence

- **Low prevalence estimate (~1.7 per million):** epidemiological modeling of clinical cases (Clarke and Ghani 2010)

- **High infection prevalence estimate (~493 per million):** tissue (appendix) surveillance for vCJD infection (UK Health Protection Agency 2012)

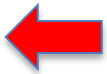
Model Results:
Risk of vCJD via Transfusion of RBC

	Mean risk per transfusion (2.5th-97.5th perc)	**Mean annual risk in 2011** (2.5th-97.5th perc) **Infections**	**Clinical cases**
Low prevalence (1.7 infections per million)	1 in 134 million (0 to 1 in 8.7 million)	0 (0-0)*	0 (0-0)*
High prevalence (493 infections per million)	1 in 480,000 (1 in 4.3 million to 1 in 111,000)	6 (0-27)	1 (0-5)

*The 2.5th and 97.5th percentiles of (0-0) indicate that in at least 97.5 percent of the model runs the risk output generated by the model was zero.

Model Validation — TTvCJD in UK and France

	Observation (cases)	Model Predicted Cases(2.5th-97.5th)	
		Low Prevalence Estimate (1.7 infections per million)	High Prevalence Estimate (493 infections per million)
UK	3	1 (0-7)	289 (3-925)
France	0	0.2 (0-0)	33 (0-0)



Low prevalence better predict clinical cases

Result Interpretation:

	Mean risk per transfusion (2.5th-97.5th perc)	**Mean annual risk in 2011** (2.5th-97.5th perc) **Infections**	**Clinical cases**
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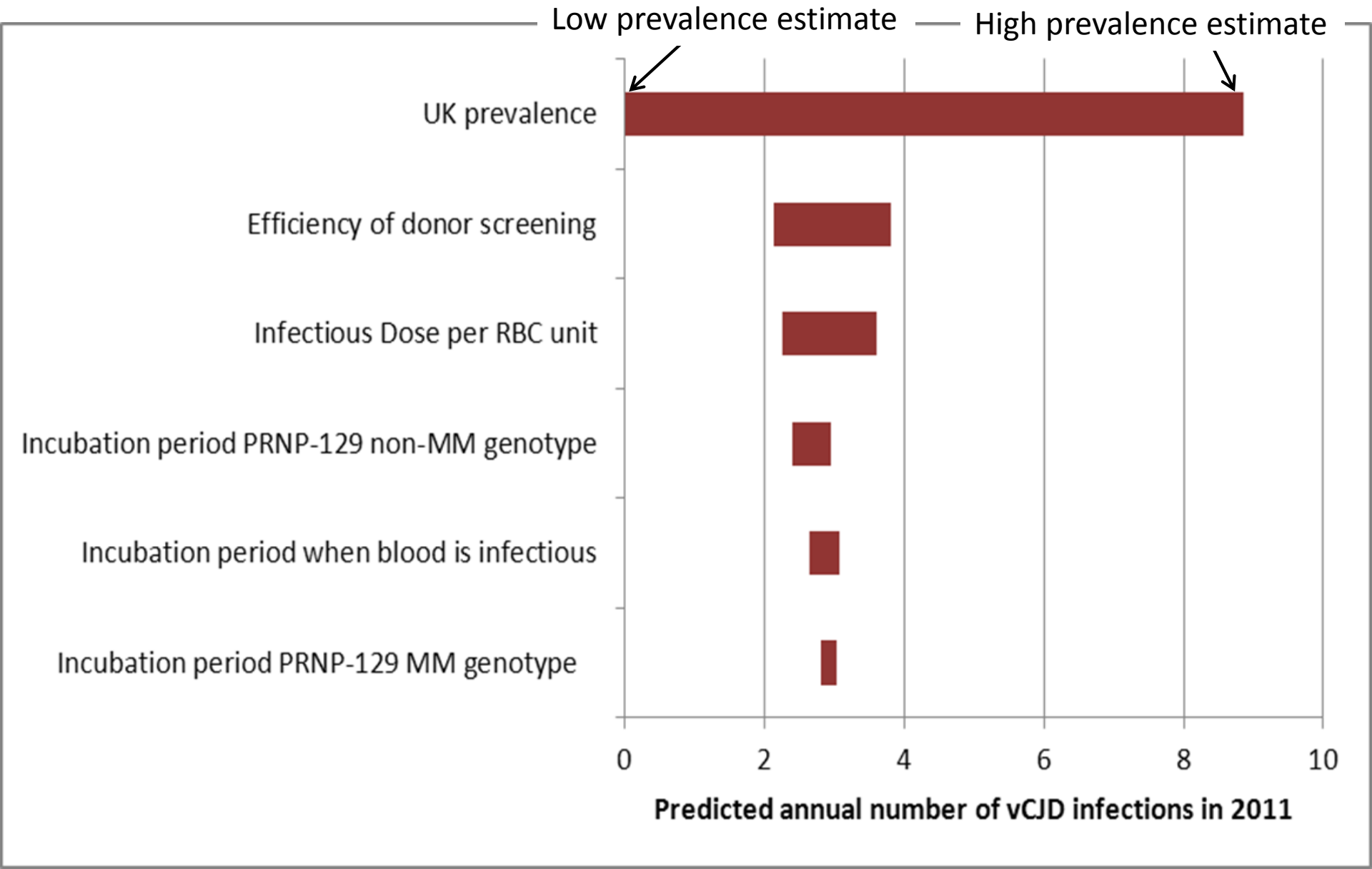
Risk of vCJD via RBC is likely small

Sensitivity/Importance Analysis



Case Study:
Geographic vCJD Risk Ranking

- Previous assessment results indicate "vCJD risk via RBC and plasma products is likely small"
- vCJD and BSE cases are decreasing worldwide
- FDA considers possible revision of donor deferral policy
- FDA developed model to rank geographic vCJD risk by
  - **vCJD case rates**
  - **Aggregated risk** (incorporating person-year exposure of travelers & Immigrants)

Model Results: Geographic Risk Ranking

	vCJD cases/million	Aggregated risk contribution
UK*	2.91	86.3%
Ireland*	0.44	2.4%
France*	0.41	6.2%
Portugal*	0.19	0.6%
Netherlands*	0.18	0.8%
Spain*	0.11	0.6%
KSA*	0.11	0.1%
Gabon	0.10	0.004%
Trinidad & Tobago	0.07	0.4%
Switzerland	0.06	0.4%
Denmark	0.05	0.2%

95%

Donor Deferral Options

Option 1 Current donor deferral policy (UK ≥3 months, 1980-1996; other countries in Europe ≥5 years, 1980-present)

Option 2 Modified donor deferral policy (UK ≥3 months, 1980-1996; Ireland & France: ≥5 years, 1980-2001)

- ✓ Lift deferral for other European countries
- ✓ Change risk period for Ireland and France from period 1980-present to period 1980-2001

Model Results: Estimated Risk Reduction & Donor Loss for Different Deferral Options

	Percentage risk reduction		Annual Donors loss
	Donor deferral only	Deferral & voluntary leukocyte reduction	
Option 1	79.0%	89.8%	254,000
Option 2	78.0%	89.3%	156,000

Option 2 offers similar risk reduction, while allowing reentry of 100,000 currently deferred donors

Summary

- FDA has used computational model to evaluate benefit-risk of donor deferral policy
- Model incorporates data uncertainty
- Models validation against external data is essential for result interpretation
- Sensitivity/importance analysis can be used to identify major risk driver and data gap
- Models help to facilitate discussion & improve communication
- Model results inform regulatory decision & help to allocate limited resource

Acknowledgements

Core working groups for FDA vCJD risk assessment:

RA for UK plasma-derived factor IX: Hong Yang, Steven Anderson, David Asher, Dorothy Scott, Mark Weinstein
RA for US plasma-derived factor VIII: Hong Yang, Richard Forshee, Mark Walderhaug, Steven Anderson, David Asher, Luisa Gregori, Pedro Piccardo, Dorothy Scott, Mark Weinstein
Estimation of variant Creutzfeldt-Jakob disease infectivity titers in human blood *(Transfusion 2014)***:** Gregori Luisa, Hong Yang and Steven Anderson
Development of dose-response models of Creutzfeldt-Jakob disease infection in nonhuman primates for assessing the risk of transfusion-transmitted variant Creutzfeldt-Jakob disease (*J Virol, 2014*): Yin Huang , Luisa Gregori , Steven Anderson, David Asher and Hong Yang.
RA for transfusion of red blood cells in the US *(Transfusion 2014)*: Hong Yang, Luisa Gregori, David Asher, Steven Anderson
Geographic risk of vCJD *(Transfusion 2017):* Hong Yang, Yin Huang, Luisa Gregori, David M. Asher, Travis Bui, Richard A. Forshee and Steven A. Anderson