Residual risk of blood borne virus infection when Australian organ donor referrals test negative: a systematic review and meta-analysis

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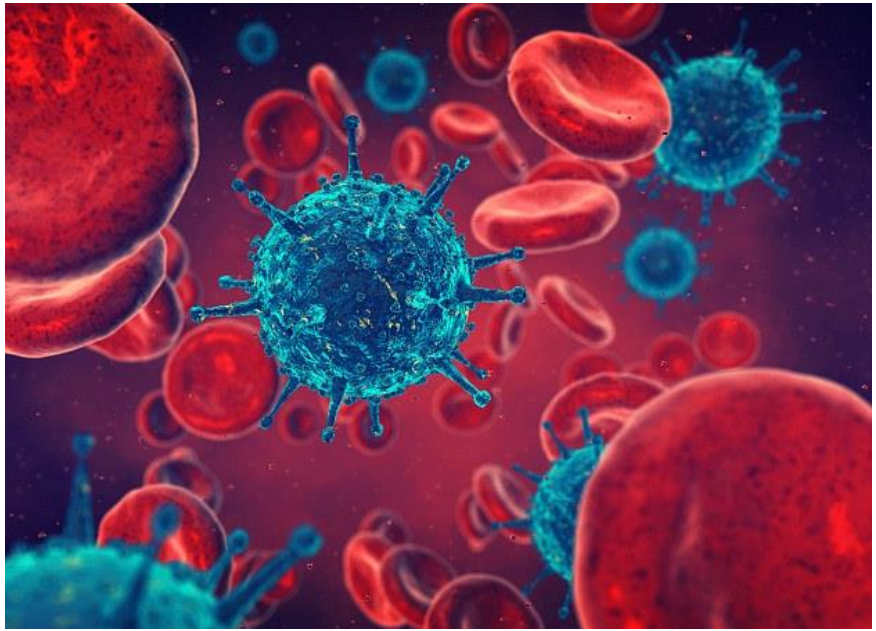

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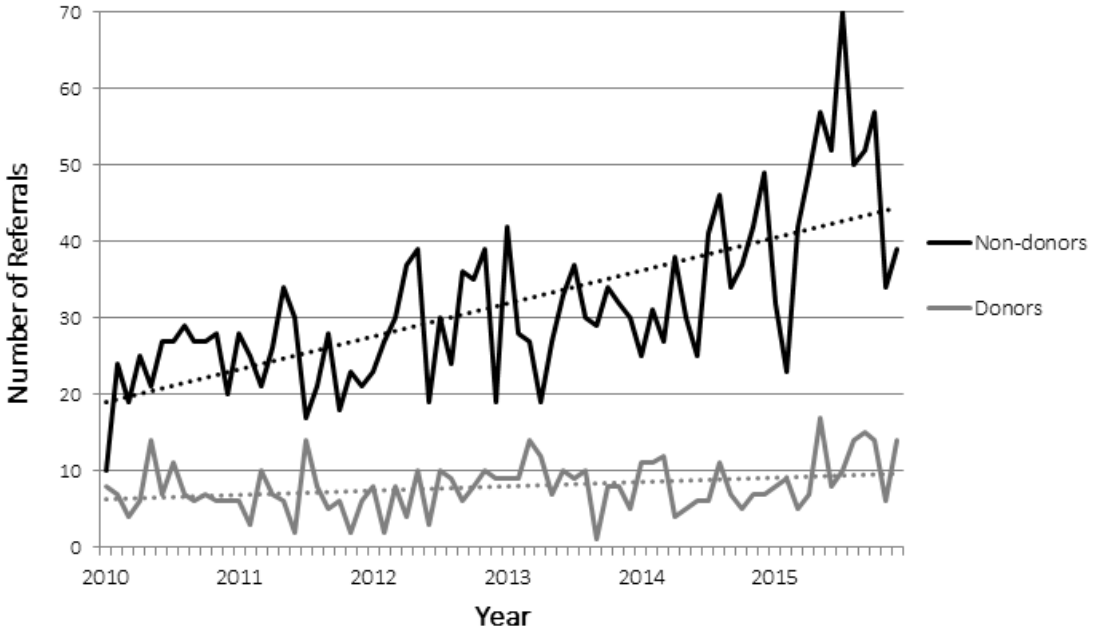
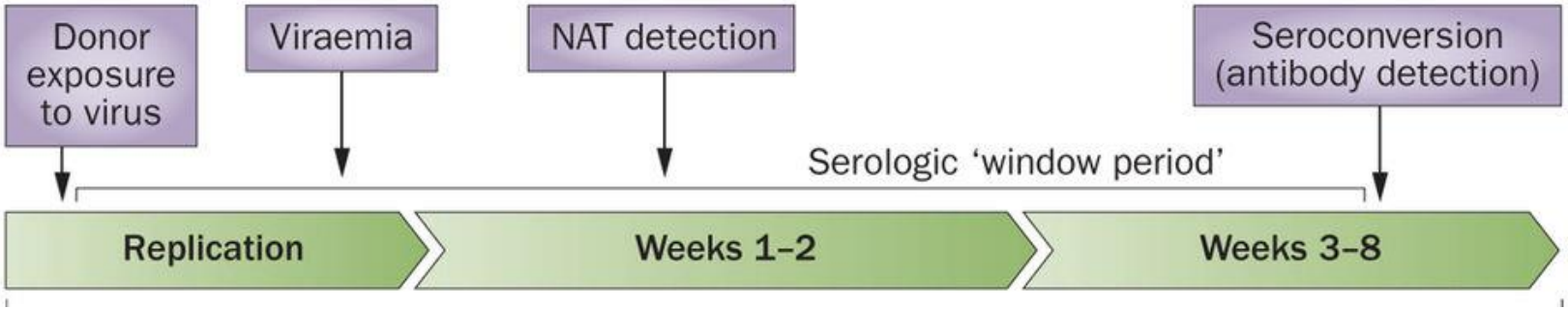
Organ shortage: Increase in referrals without increase in donor numbers

- Challenge of safely expanding donor pool
- Current donors are increasing in age, comorbidities, and DCD
- Other concerns include infection risk

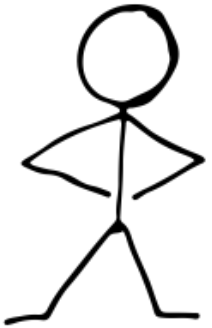


Window period infection of a blood borne virus

- Donors with risk factors are declined due to concerns of window period infection



Consider a case



- Donor referral
  - 45 year old man
  - Intravenous heroin overdose
  - No significant medical history
  - Investigations:
    - Normal renal and liver function
    - Negative serology for hepatitis B, C and HIV
- What is the risk of blood borne virus transmission to a recipient?

Aims and Hypothesis

- Estimate the prevalence and incidence of Hepatitis B, C and HIV in increased risk groups in Australia
  - Injecting drug users (IDU)
  - Prisoners
  - Men who have sex with men (MSM)
  - Sex workers
  - Sex with high risk partner
  - Known HIV blood exposure
- Calculate the residual risk of infection with negative serology +/- NAT testing

Methods

- Systematic review and meta-analysis (PROSPERO)
  - **Original estimate** of **hepatitis B, C or HIV incidence or prevalence** within an **increased risk group** in Australia
    - Including government and institute reports e.g. Kirby institute; conference abstracts; NHMRC grants
- Window period risk relates to incidence
  - Estimated pooled incidence directly where possible; where insufficient, calculated from pooled prevalence

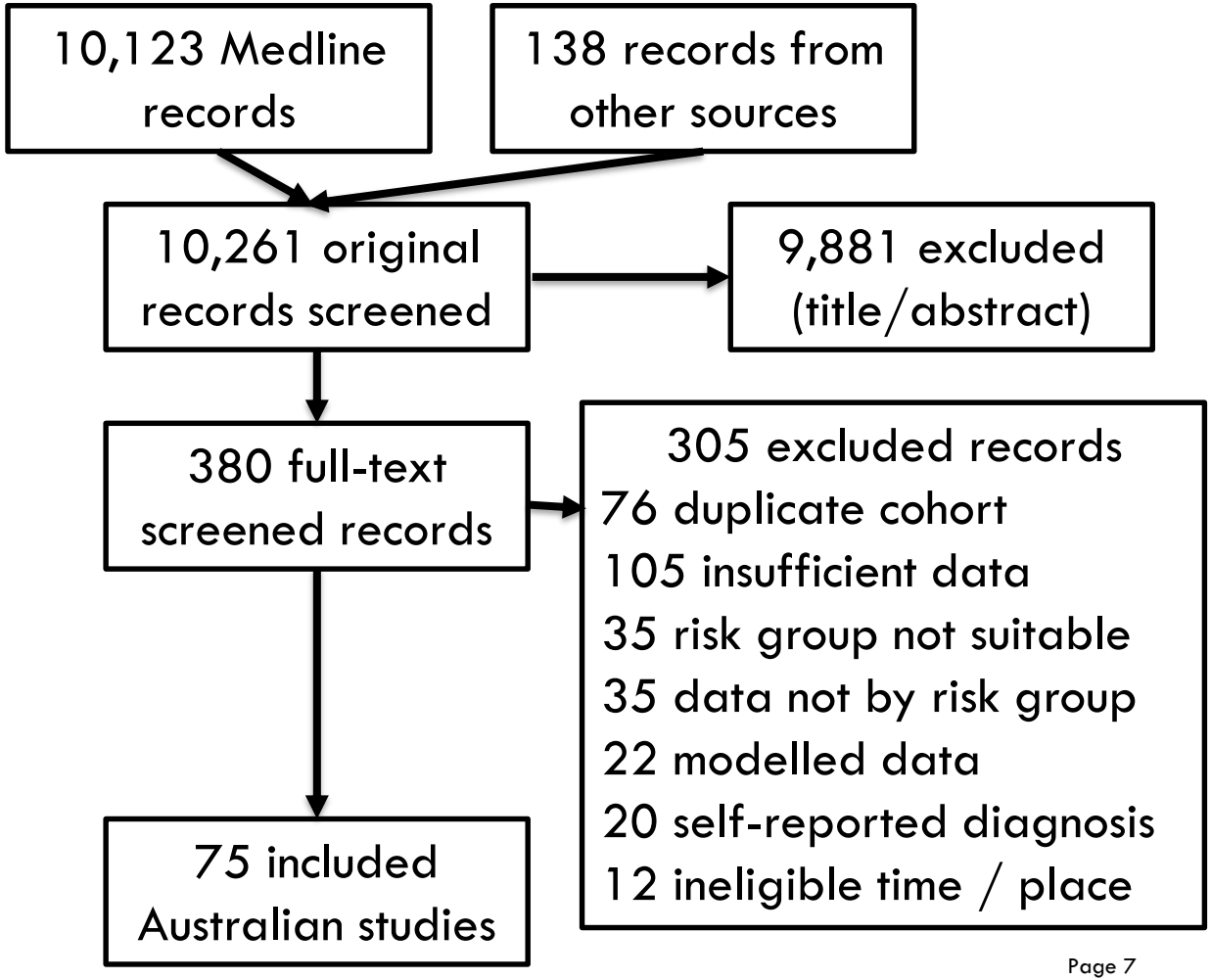
Window period (days)	Serology (ELISA)	Nucleic acid testing (NAT)
HIV	7-**22**	5-**7**
HCV	**70**	3-**5**
HBV	35-**44**	20-**22**

Ref: Humar et al, *American Journal of Transplantation* (2010)

Literature search

Exclusion criteria:

- Study published earlier than 2000
- Diagnosis of BBV not objective (e.g. self report, modelled data)
- Duplicate study cohort



Number of studies by risk group

	HIV	HCV	HBcAb	HBsAg
IDU	12	25	9	8
Prisoners	7	19	4	7
MSM	20	6	4	4
Sex workers	6	3	1	0
High risk partner	1	1	1	0

No eligible studies on HIV blood exposure

Residual HIV risk per 10,000 test-negative patients

Risk group (studies)	Patients
IDU (11)	39,814*
Prisoners (7)	10,160*
MSM (11)	62,812
Sex workers (4)	3,719*
High risk partner (1)	522*

Residual HIV risk per 10,000 test-negative patients

Risk group (studies)	Patients	Pooled incidence per 100 person-years
IDU (11)	39,814*	0.11 *(0.00-0.93)*
Prisoners (7)	10,160*	0.03 *(0.00-0.80)*
MSM (11)	62,812	0.79 *(0.44-1.15)*
Sex workers (4)	3,719*	0.03 *(0.00-0.80)*
High risk partner (1)	522*	0.03 *(0.00-0.96)*

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Australian HIV incidence is 0.005 per 100pys

Residual HIV risk per 10,000 test-negative patients

Risk group (studies)	Patients	Pooled incidence per 100 person-years	Residual risk per 10,000	
			ELISA	ELISA + NAT
IDU (11)	39,814*	0.11 *(0.00-0.93)*	**0.6** *(0.00-5.6)*	**0.2** *(0.0-1.8)*
Prisoners (7)	10,160*	0.03 *(0.00-0.80)*	**0.2** *(0.0-4.8)*	**0.1** *(0.0-1.5)*
MSM (11)	62,812	0.79 *(0.44-1.15)*	**4.8** *(2.7-6.9)*	***1.5*** *(0.9-2.2)*
Sex workers (4)	3,719*	0.03 *(0.00-0.80)*	**0.2** *(0.0-4.8)*	**0.1** *(0.0-1.5)*
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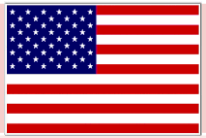
Residual HIV risk per 10,000 test-negative

Group	Serology		
			
IDU	**0.6**	12.1	6.6
Prisoner	**0.2**	2.3	1.0
MSM	**4.8**	10.2	5.8
Sex workers	**0.2**	6.6	3.7
High risk partner	**0.2**	0.7	0.7

Refs: - Kucirka et al, *American Journal of Transplantation* (2011)
- The CST/CNTRP increased risk donor working group, *Transplantation* (2014)

Residual HIV risk per 10,000 test-negative

Group	Serology			Serology + NAT		
						
IDU	**0.6**	12.1	6.6	**0.2**	4.9	2.7
Prisoner	**0.2**	2.3	1.0	**0.1**	0.9	0.4
MSM	**4.8**	10.2	5.8	**1.5**	4.2	2.4
Sex workers	**0.2**	6.6	3.7	**0.1**	2.7	1.5
High risk partner	**0.2**	0.7	0.7	**0.1**	0.3	0.3

Refs: - Kucirka et al, *American Journal of Transplantation* (2011)
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Residual HCV risk per 10,000 negative testing patients

Risk group (studies)	Patients	Residual risk per 10,000
		ELISA
		
IDU (9)	2,771	**289** *(191-386)*
Prisoners (5)	1,758	**147** *(98-195)*
MSM (5)	2,021*	**18** *(5.4-43)*
Sex workers (3)	390*	***78*** *(48-120)*
High risk partner (1)	50*	**97** *(63-143)*

Residual HCV risk per 10,000 negative testing patients

Risk group (studies)	Patients	Residual risk per 10,000		
		ELISA		
				
IDU (9)	*2,771*	**289** *(191-386)*	301	*377*
Prisoners (5)	1,758	**147** *(98-195)*	*7*	*108*
MSM (5)	2,021*	**18** *(5.4-43)*	32	*14*
Sex workers (3)	390*	***78*** *(48-120)*	115	*271*
High risk partner (1)	*50**	**97** *(63-143)*	115	*163*

Residual HCV risk per 10,000 negative testing patients

Risk group (studies)	Patients	Residual risk per 10,000					
		ELISA			ELISA + NAT		
							
IDU (9)	2,771	**289** *(191-386)*	301	*377*	**20.9** (13.8-28.0)	*32.4*	*40.8*
Prisoners (5)	1,758	**147** *(98-195)*	*7*	*108*	**10.6** *(7.0-14.1)*	*0.8*	*11.5*
MSM (5)	2,021*	**18** *(5.4-43)*	32	*14*	**1.3** *(0.4-3.1)*	*3.5*	*1.5*
Sex workers (3)	390*	***78*** *(48-120)*	115	*271*	**5.6** *(3.4-8.6)*	*12.3*	*29.1*
High risk partner (1)	*50**	**97** *(63-143)*	115	*163*	**7.0** *(4.5-10.3)*	*12.3*	*18*

Residual HBV risk per 10,000 negative testing patients

Risk group (studies)	Patients	Residual risk per 10,000
		ELISA
IDU (8)	1,859*	**98.6** *(70.9-133.5)*
Prisoners (4)	1,434*	***53.1*** *(33.3-80.3)*
MSM (3)	11,035*	**26.2** *(13.0-47.0)*
Sex workers (1)	1,089*	**6.3** *(1.1-19.6)*
High risk partner (1)	*471**	**2.2** *(0.0-13.0)*

Residual HBV risk per 10,000 negative testing patients

Risk group (studies)	Patients	Residual risk per 10,000	
		ELISA	ELISA + NAT
IDU (8)	1,859*	**98.6** *(70.9-133.5)*	**49.4** *(35.5-67.0)*
Prisoners (4)	1,434*	***53.1*** *(33.3-80.3)*	**26.6** *(16.7-40.2)*
MSM (3)	11,035*	**26.2** *(13.0-47.0)*	**13.1** *(6.5-23.5)*
Sex workers (1)	1,089*	**6.3** *(1.1-19.6)*	**3.1** *(0.5-9.8)*
High risk partner (1)	*471**	**2.2** *(0.0-13.0)*	**1.1** *(0.0-6.5)*

Residual HBV risk per 10,000 negative testing patients

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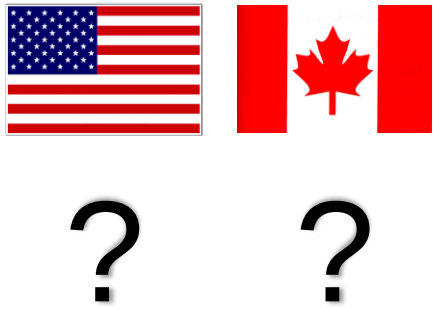
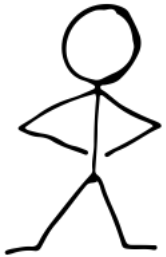


Back to our example case



- 45 year old male donor referral with recent IDU
- What is the risk to the recipient?

Most conservative estimate:

	Negative serology	Negative serology and NAT
HIV	5.6/10,000	1.8/10,000
HCV	386/10,000	28/10,000
HBV	134/10,000	67/10,000

Strengths and limitations of this research

- First national data collection, exposes important differences
- Evidence based
- Supports donation service, clinician and patient decision making
- Heterogeneity
- Sparse underlying data
- Compounded risks not calculated

Conclusion

- In increased risk groups, infection risk is higher
- However, with negative testing, absolute risks are low
  - Australian HIV risk is much lower than international populations
  - For HCV and HBV, mitigating strategies exist
- Negative NAT at referral reduces window period risk

Implications of research

- These data can be used now by donation services and clinicians
- Scope for better data to be collected in some groups
- Future work can be done eliciting patients values and preferences
- Interpretation needs understanding of competing risks, and mitigating strategies

Thank you

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Dr Tim Read
Dr Phillip Read
Dr Karen Chronister

Questions?

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Statistical methods

- Estimate pooled incidence where possible
  - Where insufficient, calculate from pooled prevalence

$$\frac{\text{Known pooled HCV incidence among IDU}}{\text{Known pooled HCV prevalence among IDU}} = \frac{\text{Unknown pooled HCV incidence in MSM}}{\text{Known pooled HCV prevalence in MSM}}$$

- Random effects model

- Calculate probability of infection within the window period

$$P(\text{Infection during WP}) = P(Y < y) = 1 - e^{-\pi d}$$

Data appraisal

- Joanna Briggs Institute Appraisal Checklist for the Systematic Review of Prevalence and Incidence Data (2014)
  - Study participant characteristics, recruitment, numbers, setting
  - Data analysis, statistical analysis, objective criteria
- Range in quality of study but overall low to medium risk bias
  - We excluded studies without objective measures
  - Key differences including study populations, recruitment and sample size
    - Outreach vs clinic; retrospective vs prospective, HIV saliva samples
    - Range in sample size 34 – 16,850
- Biases tend to over-estimate → conservative estimates