Quantifying the impact of a novel virus on the economic value of pathogen reduction technology for platelets

Adam Irving[1,2], Peter Simmonds[3], William Irving[4,5], Stephen Thomas[6,7], James Neuberger[8]

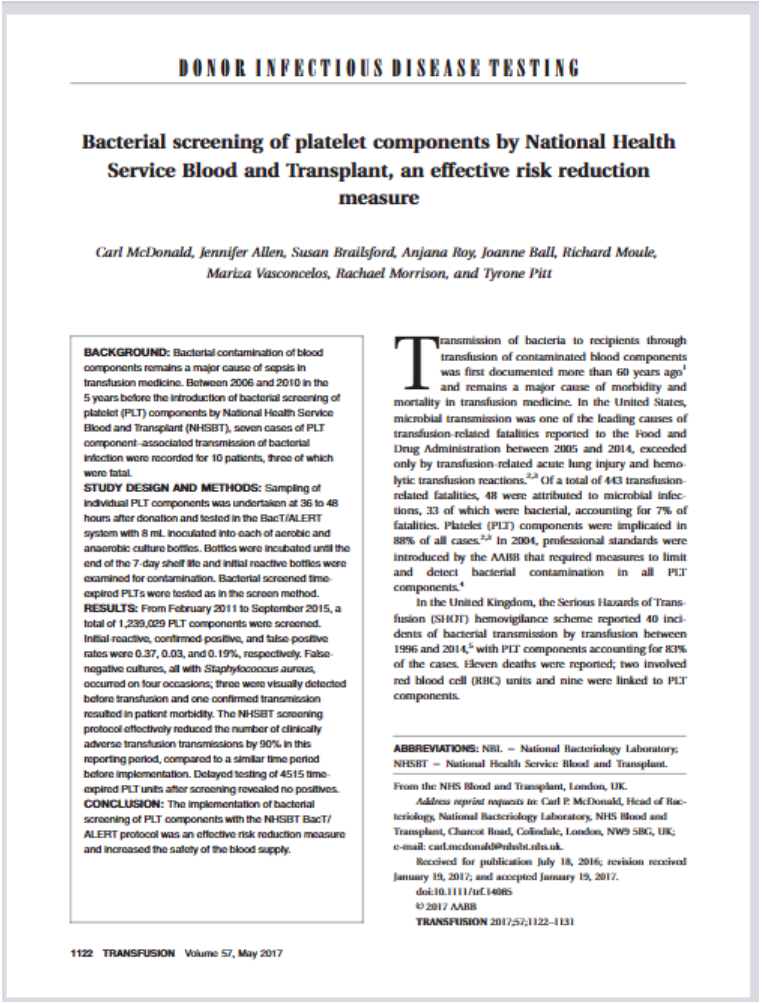
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7. NHS Blood and Transplant, London, UK
8. Queen Elizabeth Hospital, Birmingham, UK

Disclosures and disclaimers

- Chair (JN), members (PS, WI), former member now an observer (ST) of the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) but these are personal views
- The modelling work (AI) was funded by Monash University

Background

- Primary driver for implementing PR of platelets has been to mitigate the risk of bacterial transmission
- Where effective screening is already in place, the next driver for change is often cited to be protection against emerging pathogens
- This has been previously modelled in some key papers and an unpublished report, with a binary assumption regarding emergence
- We make the case for including “time to emergence” in future analysis



DONOR INFECTIOUS DISEASE TESTING

Bacterial screening of platelet components by National Health Service Blood and Transplant, an effective risk reduction measure

Carl McDonald, Jennifer Allen, Susan Brailsford, Anjana Roy, Joanne Ball, Richard Moule, Mariza Vasconcelos, Rachael Morrison, and Tyrone Pitt

BACKGROUND: Bacterial contamination of blood components remains a major cause of sepsis in transfusion medicine. Between 2006 and 2010 in the 5 years before the introduction of bacterial screening of platelet (PLT) components by National Health Service Blood and Transplant (NHSBT), seven cases of PLT component–associated transmission of bacterial infection were recorded for 10 patients, three of which were fatal.
STUDY DESIGN AND METHODS: Sampling of individual PLT components was undertaken at 36 to 48 hours after donation and tested in the BacT/ALERT system with 8 mL inoculated into each of aerobic and anaerobic culture bottles. Bottles were incubated until the end of the 7-day shelf life and initial reactive bottles were examined for contamination. Bacterial screened time-expired PLTs were tested as in the screen method.
RESULTS: From February 2011 to September 2015, a total of 1,239,029 PLT components were screened. Initial-reactive, confirmed-positive, and false-positive rates were 0.37, 0.03, and 0.19%, respectively. False-negative cultures, all with *Staphylococcus aureus*, occurred on four occasions; three were visually detected before transfusion and one confirmed transmission resulted in patient morbidity. The NHSBT screening protocol effectively reduced the number of clinically adverse transfusion transmissions by 90% in this reporting period, compared to a similar time period before implementation. Delayed testing of 4515 time-expired PLT units after screening revealed no positives.
CONCLUSION: The implementation of bacterial screening of PLT components with the NHSBT BacT/ALERT protocol was an effective risk reduction measure and increased the safety of the blood supply.

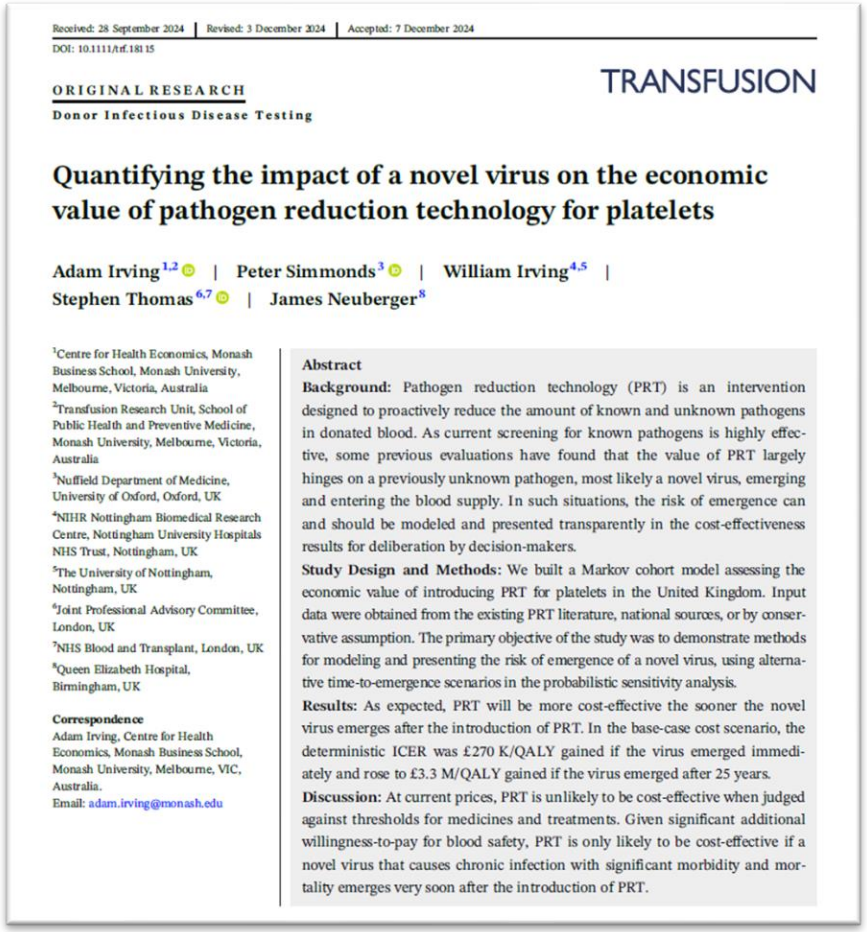
Transmission of bacteria to recipients through transfusion of contaminated blood components was first documented more than 60 years ago[1] and remains a major cause of morbidity and mortality in transfusion medicine. In the United States, microbial transmission was one of the leading causes of transfusion-related fatalities reported to the Food and Drug Administration between 2005 and 2014, exceeded only by transfusion-related acute lung injury and hemolytic transfusion reactions.[2,3] Of a total of 443 transfusion-related fatalities, 48 were attributed to microbial infections, 33 of which were bacterial, accounting for 7% of fatalities. Platelet (PLT) components were implicated in 88% of all cases.[2,3] In 2004, professional standards were introduced by the AABB that required measures to limit and detect bacterial contamination in all PLT components.[4]

In the United Kingdom, the Serious Hazards of Transfusion (SHOT) hemovigilance scheme reported 40 incidents of bacterial transmission by transfusion between 1996 and 2014,[5] with PLT components accounting for 83% of the cases. Eleven deaths were reported; two involved red blood cell (RBC) units and nine were linked to PLT components.

ABBREVIATIONS: NBL = National Bacteriology Laboratory; NHSBT = National Health Service Blood and Transplant.

From the NHS Blood and Transplant, London, UK.
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“Including *time to emergence* as a factor when…”



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DOI: 10.1111/trf.18115

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ORIGINAL RESEARCH
Donor Infectious Disease Testing

Quantifying the impact of a novel virus on the economic value of pathogen reduction technology for platelets

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Abstract

Background: Pathogen reduction technology (PRT) is an intervention designed to proactively reduce the amount of known and unknown pathogens in donated blood. As current screening for known pathogens is highly effective, some previous evaluations have found that the value of PRT largely hinges on a previously unknown pathogen, most likely a novel virus, emerging and entering the blood supply. In such situations, the risk of emergence can and should be modeled and presented transparently in the cost-effectiveness results for deliberation by decision-makers.

Study Design and Methods: We built a Markov cohort model assessing the economic value of introducing PRT for platelets in the United Kingdom. Input data were obtained from the existing PRT literature, national sources, or by conservative assumption. The primary objective of the study was to demonstrate methods for modeling and presenting the risk of emergence of a novel virus, using alternative time-to-emergence scenarios in the probabilistic sensitivity analysis.

Results: As expected, PRT will be more cost-effective the sooner the novel virus emerges after the introduction of PRT. In the base-case cost scenario, the deterministic ICER was £270 K/QALY gained if the virus emerged immediately and rose to £3.3 M/QALY gained if the virus emerged after 25 years.

Discussion: At current prices, PRT is unlikely to be cost-effective when judged against thresholds for medicines and treatments. Given significant additional willingness-to-pay for blood safety, PRT is only likely to be cost-effective if a novel virus that causes chronic infection with significant morbidity and mortality emerges very soon after the introduction of PRT.

…Quantifying the impact of a novel virus on the economic value of pathogen reduction technology for platelets

SaBTO reviews of PRT: 2014 and 2023

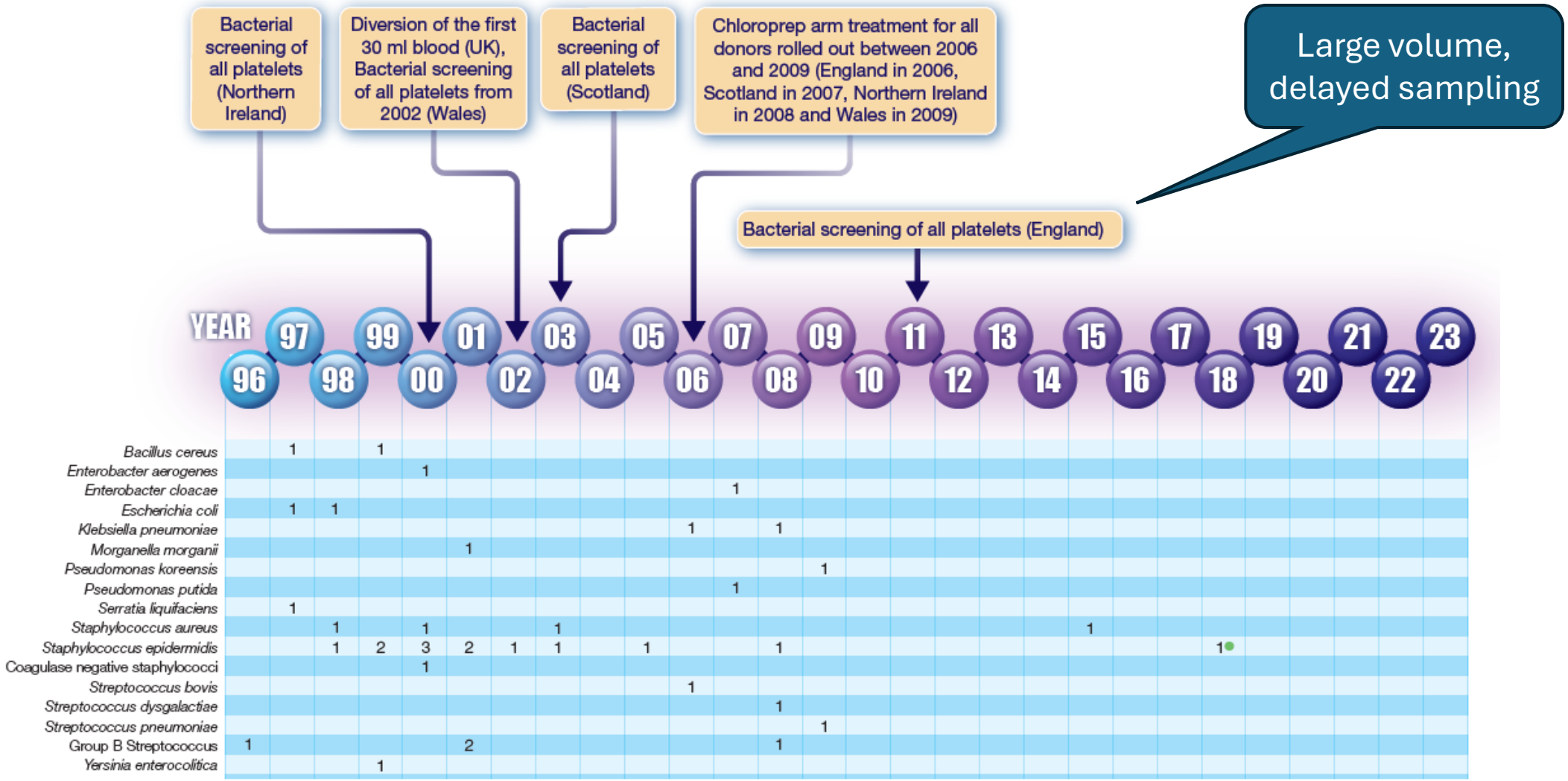
"Evidence has continued to accrue on the safety of the current bacterial screening method used by all 4 blood services in the UK. Possible benefits of PI over current methods include protection against some new and emerging transfusion transmissible infections."

- However, the impact of new infections can, at least in part, be mitigated by:
  - effective horizon scanning
  - introduction of effective deferral
  - the ability to rapidly develop diagnostic techniques
- Possible disadvantages of PI include:
  - not guaranteed to be protective
    - eg recent emerged infections such as vCJD, hepatitis E, hepatitis A
  - loss of platelet quality and quantity during processing
    - Cochrane reviews 2011, 2013, 2017 (NB update awaited)
  - cost-effectiveness continues to lie above threshold
  - significant financial and logistic implications of changing to PI



https://www.gov.uk/government/publications/pathogen-inactivation-technologies-for-platelets-sabto-advice/pathogen-inactivation-technologies-for-platelets-sabto-position-statement

Timeline of Risk Reduction Strategies and Transfusion Transmitted Infections for Bacteria, UK 1996 to 2023



SHOT Serious Hazards of Transfusion

• Transmissions are confirmed unless indicated as probable.

● Probable

https://www.shotuk.org/resources/number-of-recipients-with-confirmed-probable-transfusion-transmitted-infections-tti/

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Motivation for our model

- Some economic evaluations have results which are highly contingent on an uncertain event
  - ➢ Such as the emergence of a novel pathogen

- Previous evaluations of PRT have presented two sets of results
  1. With emergence ➤ PRT looks very cost-effective
  2. Without emergence ➤ PRT looks very cost-ineffective

- Can we improve on this, to help with our decision-making?

Objective – introduce a new consideration

- Two options for inclusion of the likelihood of the event occurring:
  1. Probability of event occurring in each year
  2. Time to the event occurring

- Preference in the health economics literature for time-to-event over probability - time is more straightforward to understand

Kleinmann *et al* 2010

THE JOURNAL OF AABB
transfusion.org
TRANSFUSION
Volume 50, Issue 12
December 2010
Pages 2592-2606

Modeling the risk of an emerging pathogen entering the Canadian blood supply

Steven Kleinman, Claire Cameron, Brian Custer, Michael Busch, Louis Katz, Boris Kralj, Ian Matheson, Ken Murphy, Jutta Preiksaitis, Dana Devine

First published: 03 December 2010 | https://doi.org/10.1111/j.1537-2995.2010.02724.x | Citations: 34

- On behalf of CBS, Kleinman *et al* constructed a model to demonstrate how newly emerging pathogens might affect blood transfusion recipients in Canada
- Modelled acute and chronic infections
- Emergence over a 3 to 10 year range, 5 years the most likely
- Looked at all components and the impact of PRT
  - 20% reduction in cases and in subsequent medical costs

Gregoire *et al* 2022

THE JOURNAL OF AABB transfusion.org
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TRANSFUSION COMPLICATIONS | Full Access

Cost-effectiveness of pathogen reduction technology for plasma and platelets in Québec: A focus on potential emerging pathogens

Yves Grégoire, Gilles Delage, Brian Custer, Samuel Rochette, Christian Renaud, Antoine Lewin, Marc Germain

First published: 13 May 2022 | https://doi.org/10.1111/trf.16926 | Citations: 4



Volume 62, Issue 6
June 2022
Pages 1208-1217

On behalf of HQ, Gregoire *et al* modelled acute and chronic infections, in three scenarios

Base case: incremental cost-effectiveness ratio (ICER) of PRT estimated at approx. £4,300,000 /QALY gained

In scenarios assuming the presence of an HIV-like pathogen, the ICER was:

- £66,000 /QALY gained in the “highly contagious” scenario
- £143,000 /QALY gained in the “average transmission” scenario
- £687,000 /QALY gained in the “rapid testing” scenario

Cerus technical report (BresMed, 2020)



- Used some data provided by NHSBT
- Unpublished but shared
- The emerging threat risk is a key model parameter
- For INTERCEPT, there is assumed to be zero risk of transmission based on its efficacy against chikungunya virus
- For the comparator arm, emerging threat incidence was calculated based on Kleinman *et al* 2010

Cerus technical report (BresMed, 2020)

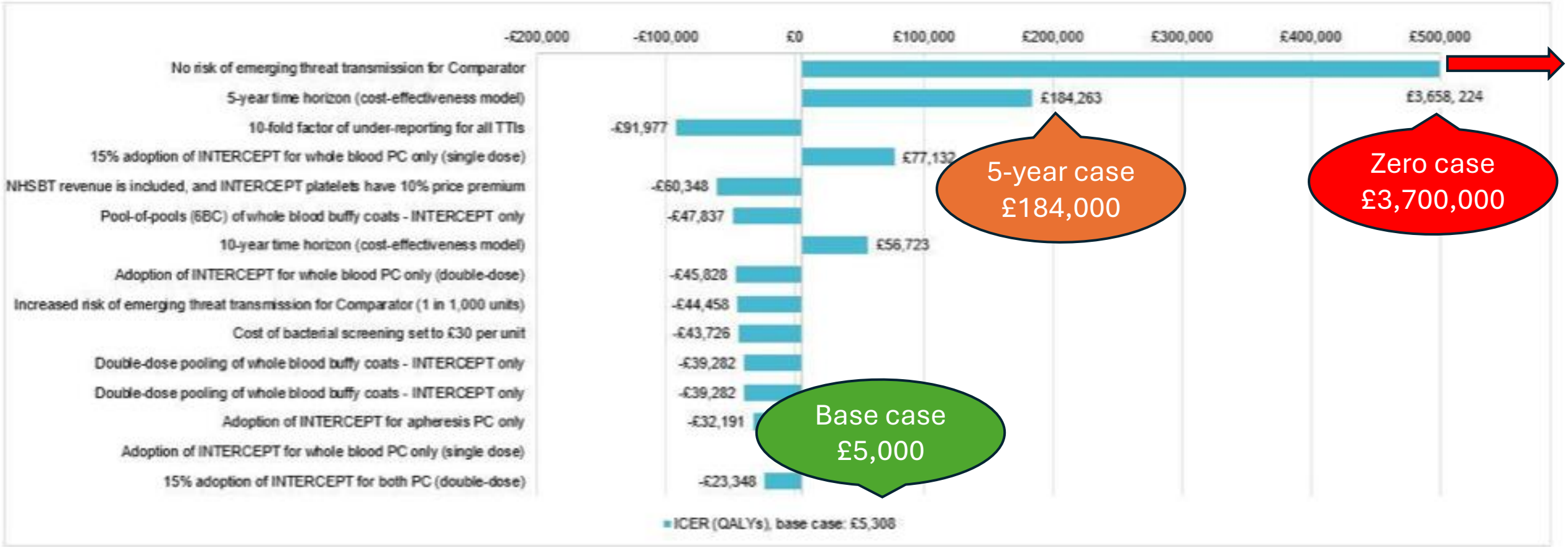
2651: Health Economic Analysis of INTERCEPT® Blood System for Pathogen Inactivation of Platelets

Model technical report

Report details

Report Version 4, 25 August 2020

Figure 23: Scenario analysis, top 15 most impactful scenarios (absolute change from base case ICER)



Notes from the virologists

- With the exception of HIV-1 and HIV-2, recent zoonotic viruses do not cause chronic infections
  - Evidenced by the acute / resolving nature of infections with SARS-CoV-2, SARS-CoV, MERS-CoV, any form of IAV, Nipah, Hendra, or any arbovirus
- HIV-1 is highly unusual
  - establishing initially asymptomatic infections in humans
  - HIV-1 has probably been spilling over into humans from the early 20th Century and underwent a series of adaptive mutations for human infection and transmission over the following fifty years.
  - in modelling terms, you might conservatively assign this as a once in a century event
- HIV-2
  - has probably been spilling over into humans in West Africa for centuries or millennia
  - As with HIV-1, changes in travel and demographics led to its spread into certain Western countries but with minimal clinical impact
- HBV and HCV
  - are not emerging or zoonotic infections and have probably always infected humans
  - current screening is fully adequate to prevent their transfusion transmission

Modern surveillance and detection

- Many surveillance schemes are in place
- Next generation sequencing is able to detect new viruses
  - But has its challenges…
- Repeated application of NGS to human blood samples has so far provided no evidence for the existence of any other persistent virus infecting humans (and blood donors) beyond:
  - human pegivirus (believed non-pathogenic)
  - anelloviruses (non-pathogenic)
  - various reactivations of host-adapted human DNA viruses (polyomaviruses, parvoviruses, papillomaviruses, herpesviruses)
- If there was a virus like HIV in donors, it would have been detected by now, wouldn't it…?

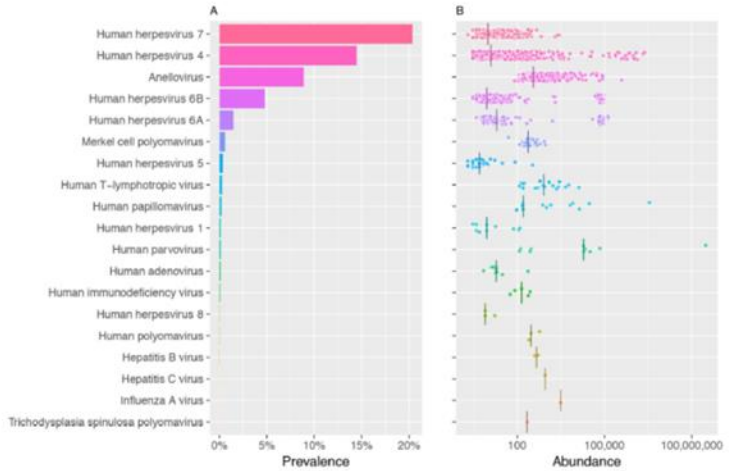


Fig 3. Prevalence and abundance of human DNA viruses and retroviruses in 8,240 individuals. A. Frequency of 19 human viruses in the study population ranked according to their prevalence. **B.** The viral load of human viruses represented on the x-axis as genome copies per 100,000 human cells; the bar represents the median.

https://doi.org/10.1371/journal.ppat.1006292.g003

PLOS PATHOGENS

RESEARCH ARTICLE

The blood DNA virome in 8,000 humans

Ahmed Moustafa[1], Chao Xie[2], Ewen Kirkness[1], William Biggs[1], Emily Wong[1], Yaron Turpaz[2], Kenneth Bloom[1], Eric Delwart[3], Karen E. Nelson[4], J. Craig Venter[1,4]*, Amalio Telenti[1,4]*

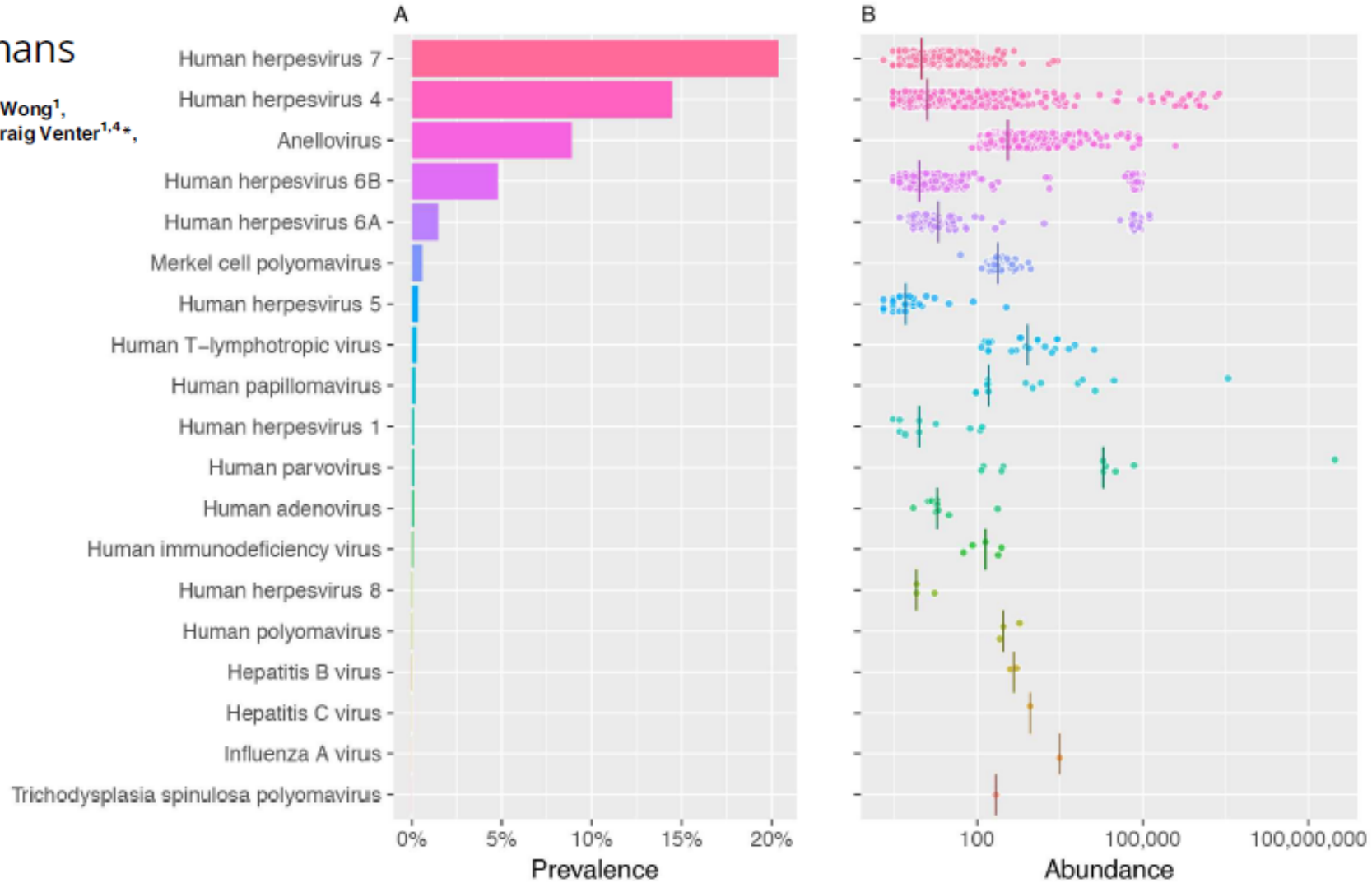


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https://doi.org/10.1371/journal.ppat.1006292.g003

A quick Wiki of COVID-19 test development

January 2020

10 Jan – Chinese scientists published the first genetic sequences of SARS-CoV-2

10 Jan - Public Health England announced a test using a real-time RT-PCR assay based on oral swabs. Rolled out to 12 labs across the UK on 10 Feb

10 Jan - Malaysian Institute for Medical Research produced "primers and probes“.

17 Jan - German nucleic acid testing protocol published.

23 Jan - early PCR test developed by Charité University Hosp Berlin, basis of 250,000 kits distributed by WHO

24 Jan - Russian COVID-19 test entered production after development by the State Research Center of Virology and Biotechnology

28 Jan - US CDC developed its SARS-CoV-2 Real Time PCR Diagnostic Panel and published its protocol

February 2020

4 Feb - South Korean Kogenebiotech's clinical grade, nucleic acid test was approved by Korean Center for Disease Control and Prevention

5 Feb - in Wuhan, BGI opened a 2000-sq-meter emergency detection laboratory, followed by labs in 12 cities across China.

11 Feb - test approved by the Federal Service for Surveillance in Healthcare in Russia

28 Feb - US FDA test approval under an EUA

March 2020

4 March - China reached 50,000 tests per day

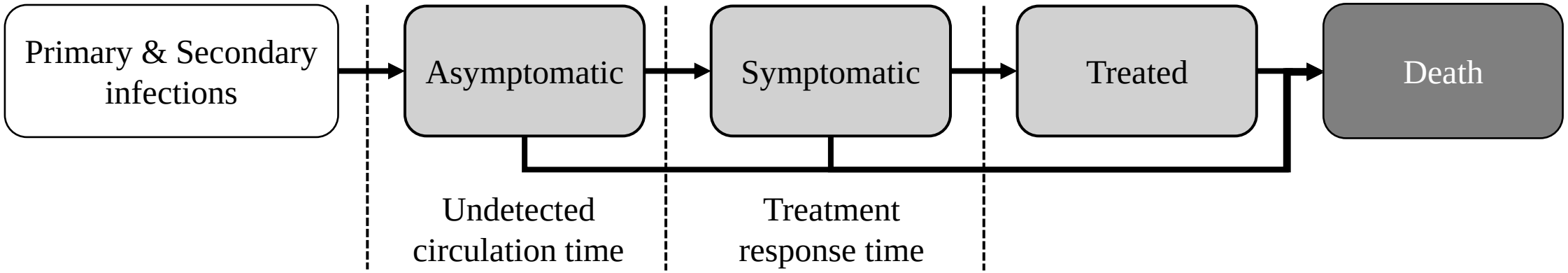
5 March - US commercial labs began testing. In March, the FDA issued EUAs for nucleic acid tests to at least 5 companies

12 March - Mayo Clinic announced a nucleic acid test



https://en.wikipedia.org/wiki/Development_of_COVID-19_tests

Back to the model...



Inputs



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Parameter	Min	Mode	Max	Source
Prevalence in donated blood per 10,000 components	1	4.5	8	Kleinman 2010
Rate of secondary transmission per primary infection	2%	8.5%	15%	Kleinman 2010
Undetected circulation time (years)	1	3	5	Assumption
Treatment response time (years)	3	5	10	Kleinman 2010
Additional mortality risk (per year)	1%	5%	10%	Assumption

Parameter	Distribution	Mean	SE	Source
Price of PRT/unit	Gamma	£75	£15	Grégoire 2022
Annual cost of Asymptomatic	Gamma	£0	£100	Assumption
Annual cost of Symptomatic	Gamma	£1,000	£500	Assumption
Annual cost of Treated	Gamma	£11,000	£5,500	Terrence Higgins Trust
Utility weight for Asymptomatic	Beta	0.86	0.004	Miners 2001
Disutility for Symptomatic	Beta	0.21	0.105	Miners 2001
Disutility for Treated	Beta	0.11	0.055	Miners 2014
Utility weight for No Infection	Beta	0.86	0.004	Miners 2001

£40
(Graz, AU)

Results



ORIGINAL RESEARCH
Donor Infectious Disease Testing

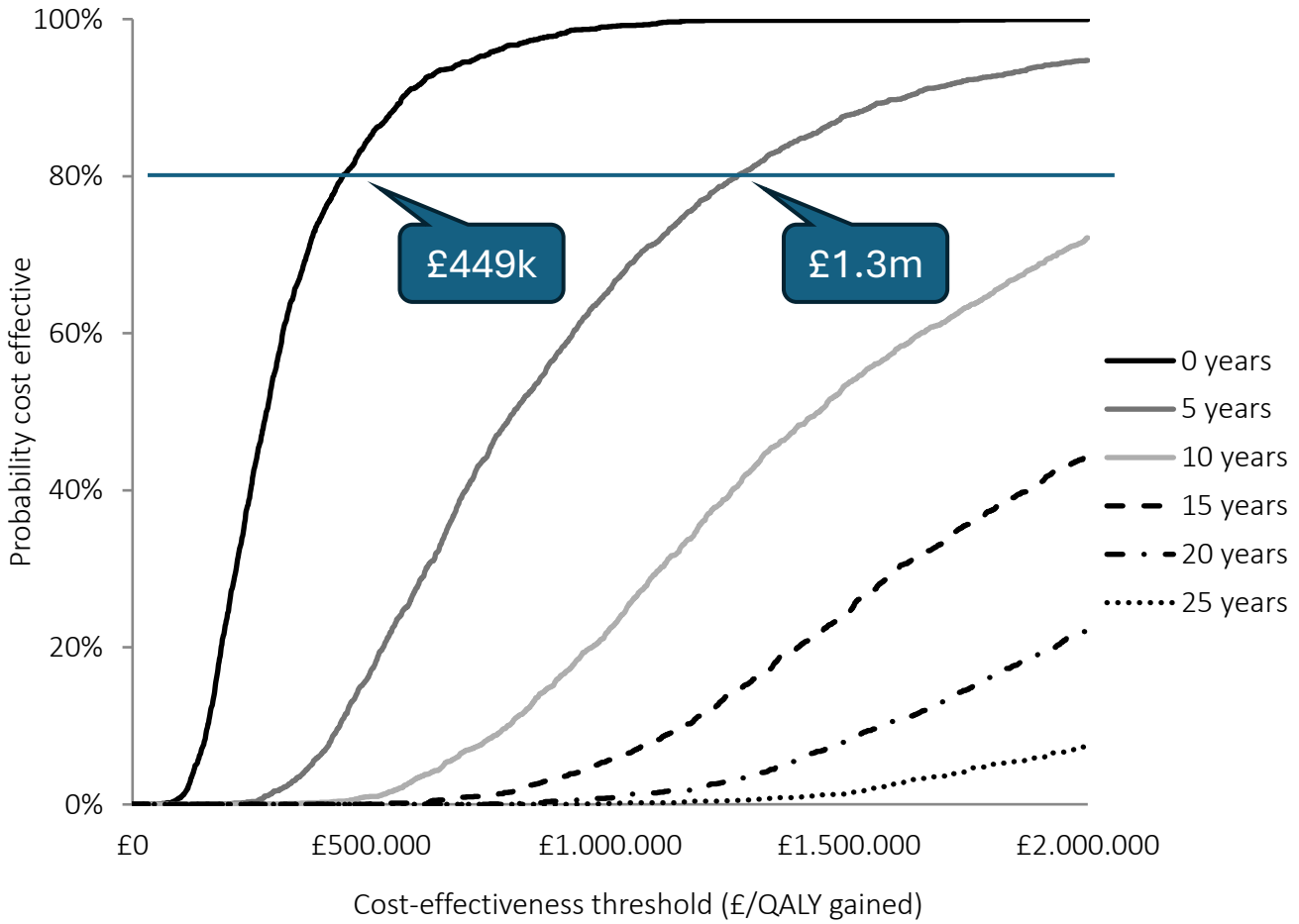
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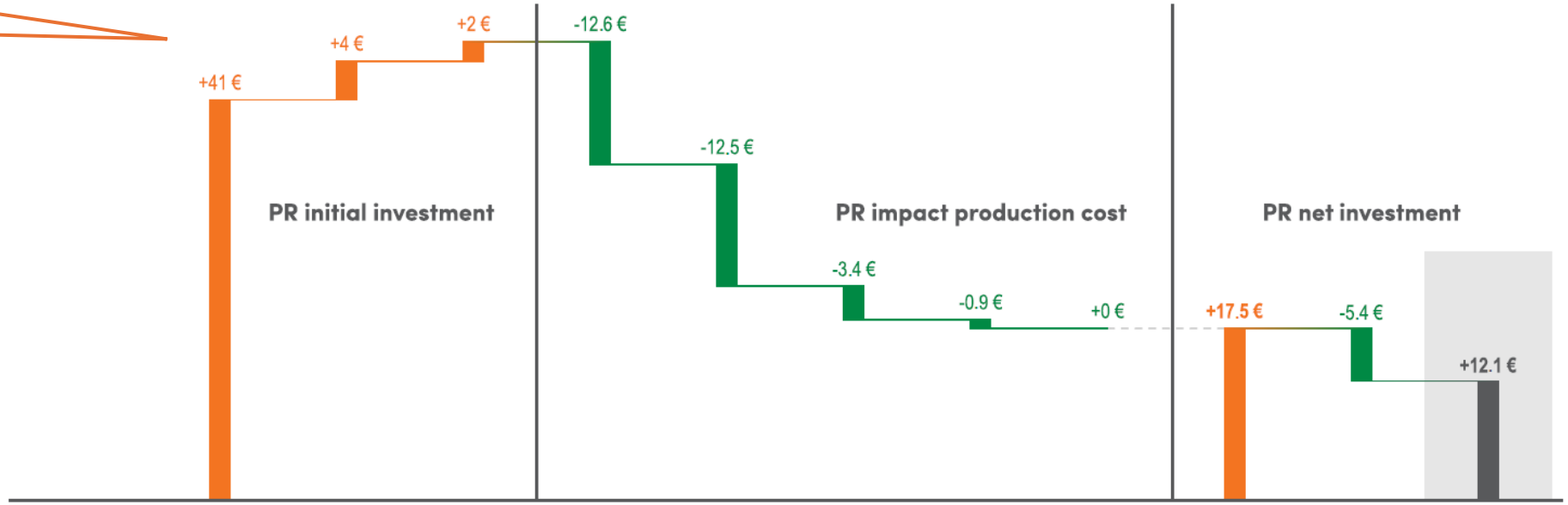
Time to Emergence	Incremental Cost-effectiveness Ratio
0 years	£270,282
5 years	£690,121
10 years	£1,188,869
15 years	£1,781,617
20 years	£2,486,794
25 years	£3,327,167

Probabilistic Sensitivity Analysis:
Cost Effectiveness Acceptability Curves



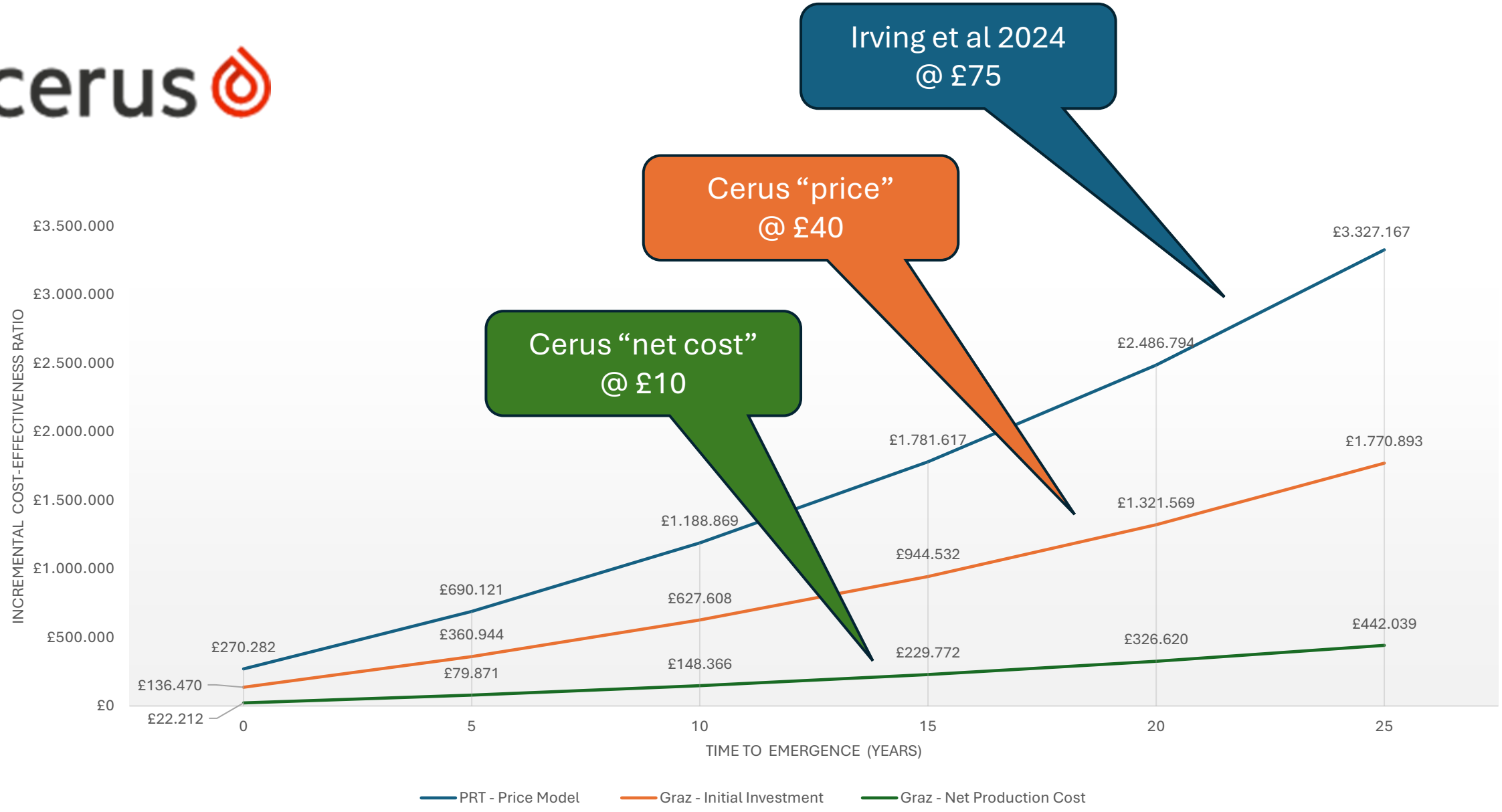
Graz-case
Cheaper purchase price: £40 v £75
Net Production Cost increase per unit: £10 vs £75

€47 = £40



	Disposables: Safety measures	Labor	Maintenance and depreciation illuminator	Outdating PCs in inventory	Disposables: Pooling cost	Gamma irradiation	Scrap rate during production	Testing (including quality control)	NET PRODUCTION COSTS	INCREMENTAL REVENUE PLASMA FOR ` FRACTIONATION	NET PRODUCTION COST minus INCREMENTAL REVENUE
Pre-PR (in €)	20.1	7.7	0	22.2	33.5	3.4	8.8	66.9	162.6	231.2	
PR period (in €)	**61**	**11.7**	**2**	**9.6**	**21**	**0**	**7.9**	**66.9**	**180.1**	**236.6**	
Evolution of PR period vs. Pre-PR (in %)	+25.2%	+2.5%	+1.2%	-7.8%	-7.7%	-2.1%	-0.6%	+0%	+10.8%	+2.3%	+7.5%

Reference: Pathogen reduction of double-dose platelet concentrates from pools of eight buffy coats: Product quality, safety, and economic aspects; Konrad Rosskopf et al; Department of Blood Group Serology and Transfusion Medicine, Medical University Graz and LKH-Univ.Klinikum Graz, Austria; Transfusion 2020 Sep: 60 (9):2058-2066



Reference: Pathogen reduction of double-dose platelet concentrates from pools of eight buffy coats: Product quality, safety, and economic aspects; Konrad Rosskopf et al; Department of Blood Group Serology and Transfusion Medicine, Medical University Graz and LKH-Univ.Klinikum Graz, Austria; Transfusion 2020 Sep: 60 (9):2058-2066

Conclusions

- Time to emergence is a valid consideration
- Our model makes a minor contribution
  - Provides a novel way of presenting results, in a standard graphical format
  - An alternative presentation could consider probabilities of emergence in each year
- We do not attempt to capture the full risks and rewards of PRT
  - These can be factored in, the model is available for use
  - Publication has already advanced the discussion, providing new figures for consideration and discussion

Thank you for your attention