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Journal

Blood Transfusion, 16(2)

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Publication Date

2018-02-01

DOI

10.2450/2016.0130-16

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Cost-utility and budget impact of methylene blue-treated plasma compared to quarantine plasma

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Background. Methylene blue and visible light treatment and quarantine are two methods used to reduce adverse events, mostly infections, associated with the transfusion of fresh-frozen plasma. The objective of this study was to estimate and compare the budget impact and cost-utility of these two methods from a payer's perspective.

Materials and methods. A budget impact and cost-utility model simulating the risks of hepatitis B virus, hepatitis C virus, cytomegalovirus, a West Nile virus-like infection, allergic reactions and febrile non-haemolytic transfusion reactions achieved using plasma treated with methylene blue and visible light (MBP) and quarantine plasma (QP) was constructed for Spain. QP costs were estimated using data from one blood centre in Spain and published literature. The costs of producing fresh-frozen plasma from whole blood, apheresis plasma, and multicomponent apheresis, and separately for passive and active methods of donor recall for QP were included. Costs and outcomes over a 5-year and lifetime time horizon were estimated.

Results. Compared to passive QP, MBP led to a net increase of € 850,352, and compared to active QP, MBP led to a net saving of € 5,890,425 over a 5-year period. Compared to passive QP, MBP increased the cost of fresh-frozen plasma per patient by € 7.21 and had an incremental cost-utility ratio of € 705,126 per quality-adjusted life-year. Compared to active QP, MBP reduced cost by € 50.46 per patient and was more effective.

Discussion. Plasma collection method and quarantine approach had the strongest influence on the budget impact and cost-utility of MBP. If QP relies on plasma from whole blood collection and passive quarantine, it is less costly than MBP. However, MPB was estimated to be more effective than QP in all analyses.

Keywords: plasma, pathogens, adverse events, costs and cost analysis.

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Introduction

There is a range of pathogen inactivation technologies which are approved and used to treat blood components in Europe[1]. Methylene blue and visible light treatment and quarantine are two common methods used to reduce the risk of adverse events associated with plasma transfusion in Spain and in other countries. Each method has attendant costs and possibly different adverse event implications for recipients[2,3]. Fresh-frozen plasma (FFP) can be derived from whole blood (WB) or apheresis plasma collections. The available methods for improving plasma safety also have consequences for secondary use of FFP. For example, methylene blue and visible light-treated plasma (MBP) cannot be used for recovered plasma fractionation. In addition, each inactivation method may lead to alterations in the relative activity of therapeutic plasma proteins[2], although evidence of increased plasma transfusion with the use of MBP compared to FFP has not been documented. On the other hand, quarantine plasma (QP) involves establishing the procedures for quarantine, the physical capability to store FFP for longer terms while in quarantine and the processes for donor recall that permit the release of FFP for transfusion. Blood centres in Spain use different approaches to collect plasma, but the majority of FFP is obtained from WB donations.

Similarly, blood centres may use different security measures with respect to quarantine. Quarantine relies on donors coming back to make a new blood donation or to provide a sample for testing before the stored FFP can be cleared for release. Passive quarantine relies on donors returning for the subsequent donation with

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no mechanism, such as calling the donors, to seek the donors' return. Active quarantine is where donors are contacted and asked to return as early as allowed in the quarantine period: maintaining such a programme requires human and other resources.

The risk of adverse outcomes for recipients of MBP or QP is not the same. MBP may have advantages in two areas. First, in the area of any type of infection for which donor screening is not or is only partially in place, and particularly for emerging infections that may have asymptomatic phases of infection such as West Nile, dengue and Zika viruses[4]. Second, the available evidence demonstrates that the risk of allergic and other non-infectious reactions is lower for MBP than for QP[5,6].

The Alliance of Blood Operators Risk-Based Decision-Making initiative recently published recommendations for health economics and outcomes analysis of blood safety technologies[7]. While these are consensus recommendations, which may not be applicable to all settings, two evaluation methods were recommended because of the complimentary health economic information they contribute to decision-making in the field of blood safety. The first method is used to assess the costs that accrue or are expected to accrue when an intervention is implemented; budget impact analysis (BIA) measures resource use and provides results in terms of the costs incurred or saved by adopting an intervention from the standpoint of the budgeting authority or health care decision-maker. The second methodology is used to assess value gained for resources spent; cost-utility analysis (CUA) where value for money is assessed in terms of cost per quality-adjusted life-years (QALY) gained. The objective of our study was to estimate the budget impact and cost-utility (sometimes known as cost-effectiveness), from a payer's perspective, of using MBP compared to QP for the reduction of pathogens and adverse events related to transfused plasma in Spain considering different approaches to plasma collection and the costs of MBP and QP.

Materials and Methods

Model structure

We developed a decision analytic model in Microsoft Excel (2011) to estimate the costs, outcomes, and budget impact of transfusing patients with MBP and QP in Spain. The model combined a "frontend" decision tree and two "backend" Markov models. The decision tree (Figure 1) was used to model: (i) hepatitis B or C virus infection (HBV, HCV) with risk of rapid liver failure, (ii) human immunodeficiency virus (HIV) infection, (iii) cytomegalovirus (CMV) infection (asymptomatic CMV, CMV retinitis, and CMV mononucleosis), (iv) a West Nile virus (WNV)-like emerging infection (asymptomatic, WNV fever and chronic neuro-invasive disease), (v) severe and non-severe allergic reactions, and (vi) febrile non-haemolytic transfusion reactions (FNHTR). We assumed that patients would not simultaneously experience more than one adverse event. Markov models (Online Supplementary Figure S1) were used to simulate the costs and outcomes of chronic hepatitis B and C, and HIV infection. The hepatitis Markov model (Online Supplementary Figure S1A) had ten states (chronic hepatitis, compensated cirrhosis, hepatocellular carcinoma, oesophageal varices, hepatic encephalopathy, ascites, three liver transplant states, and death). The HIV Markov model (Online Supplementary Figure S1B) had four states (HIV, chronic HIV, AIDS, and death). The cycle length for Markov modelling was 1 year and the time horizon of the analysis was lifetime. For all other adverse events we assumed that the consequences would occur within the first year except for the sequelae of WNV neuro-invasive disease, which could last a lifetime.

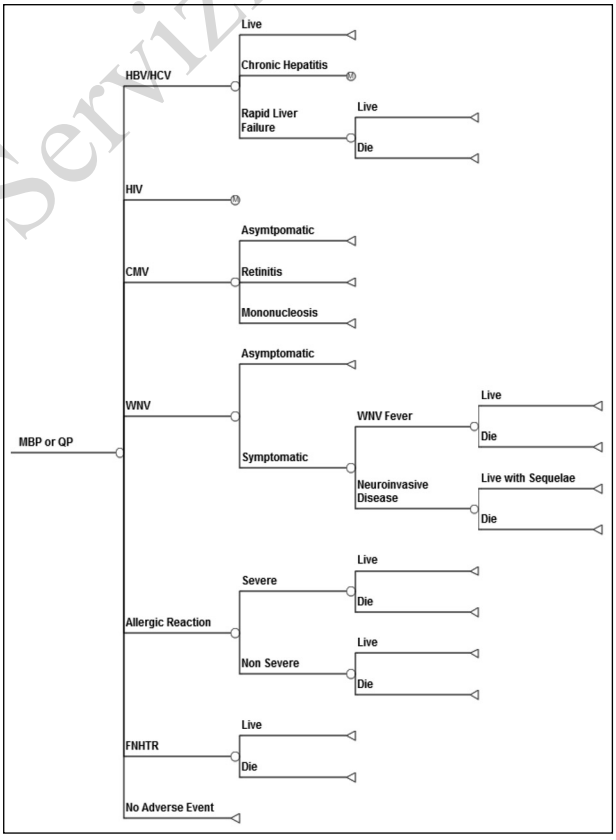

Figure 1 - Decision tree of adverse events and outcomes of plasma transfusion.
MBP: methylene blue- and visible light-treated plasma; QP: quarantine plasma; HBV: hepatitis B virus; HCV: hepatitis C virus, HIV: human immunodeficiency virus, CMV: cytomegalovirus, WNV: West Nile virus; FNHTR: febrile non-haemolytic transfusion reaction.

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Event probabilities

To estimate probabilities of adverse events, we used haemovigilance data on MBP and QP collected over 11 years in Greece[6] except for the annual probability of WNV for transfused QP (assumed to be 0.0005) and HIV for both transfused MBP and QP. For the annual probability of HIV, we used a recent publication from Spain which reported the first case of breakthrough HIV infection using MBP[8] and the estimated number of MBP transfusions during the same time period based on MBP kit distribution data. Adverse event probabilities are summarised in Table I.

We used publically available literature to estimate transition probabilities for the Markov models. These probabilities are summarised in the Online Supplementary Table SI. We estimated background post-transfusion mortality from population-based studies of survival[9-11]. Post-transfusions survival data are from sources outside Spain.

Outcomes

To estimate QALY, we obtained health state utilities for adverse events, infections, and their sequelae from the published literature, supported by assumptions where estimates were unavailable. Health state preference weight utility estimates are summarised in the Online Supplementary Table SII.

Costs

We estimated costs from the payer's perspective and included costs of production of MBP and QP, and the management of adverse events. All costs were adjusted to the year 2014 using the Consumer Price Index for healthcare in Spain. Future costs were discounted at 3% *per annum*. The estimate of the mean costs of MBP and QP per patient assumes a single transfusion episode using four FFP units.

We estimated the costs of producing FFP from WB, by apheresis plasma, and by multicomponent apheresis, and separately for the passive and active methods of donor recall. To estimate the costs of FFP production, we used the approach described by Eandi and colleagues[12]. According to their method, the cost per unit of transfusable plasma is calculated by adjusting the cost of obtaining a litre of plasma by the mean plasma yield and the mean number of 200 mL-containing units that can be obtained using WB, apheresis plasma, and multicomponent apheresis.

To estimate the costs of QP, we used volume and costs (handling and storage) estimates from a single blood centre in Spain. This centre processes 65,000 WB donations plus 2,500 apheresis collections per year. Approximately 8,000 units of plasma (280 mL each) are released to hospitals each year. We adjusted costs to account for the proportion of QP FFP units from non-returning donors that are sold for fractionation. For QP, we accounted for the costs of donor recall and retesting in the active donor recall scenario, the loss rates from donors who do not return for testing, and loss rates due to handling. For MBP, data were based on the Macopharma system[13]. We assumed no additional storage and handling costs for MBP beyond FFP storage. The parameters for the estimation of the costs of MBP and QP are summarised in Table II.

We used data from the published literature to estimate the costs of managing adverse events and treating breakthrough infections using country-specific data where possible. These data are summarised in Table II.

Budget impact

We estimated the budget impact of MBP and QP over a 5-year time horizon. We projected the number of plasma transfusions using the overall population of

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Table I - Annual residual risks of plasma transfusion-related adverse events.

Adverse event	QP		MBP	
	Value	*Source*	*Value*	*Source*
HBV	0.0000001	Politis *et al.*[5]	0.00000001	Politis *et al.*[6]
HCV	0.0000001	Politis *et al.*[5]	0.00000001	Politis *et al.*[6]
HIV	0.0000001	Politis *et al.*[5]	0.00000005	Álvarez *et al.*[8]
CMV	0.000001	Politis *et al.*[5]	0.00000001	Politis *et al.*[6]
WNV-like	0.00005	Custer *et al.*[5]	0.00000001	Politis *et al.*[6]
Non-severe allergic reaction	0.00495	Politis *et al.*[5]	0.0000037	Politis *et al.*[6]
Severe allergic reaction	0.0002127	Politis *et al.*[5]	0	Politis *et al.*[6]
FNHTR	0.0007	Politis *et al.*[5]	0.0001	Politis *et al.*[6]

All probabilities were varied by ±20% for sensitivity analyses. QP: quarantine plasma; MBP: methylene blue- and visible light-treated plasma; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; CMV: cytomegalovirus; WNV: West Nile virus; FNHTR: febrile non-haemolytic transfusion reaction.

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Table II - Parameters used to estimate plasma production and storage costs.

Parameter	Value (range)	Source
Cost of production for 1 litre of plasma, €		
Whole blood	113 (90, 135)	Eandi *et al*.[12]
Plasma apheresis	284 (227, 341)	Eandi *et al*.[12]
Multicomponent apheresis	183 (146, 220)	Eandi *et al*.[12]
Mean plasma yield per donation, mL		
Whole blood	270 (216, 324)	Eandi *et al*.[12]
Plasma apheresis	600 (480, 720)	Eandi *et al*.[12]
Multicomponent apheresis	399 (320, 478)	Eandi *et al*.[12]
Units of transfusable plasma		
Whole blood	1	Assumption
Plasma apheresis	3	Assumption
Multicomponent apheresis	2	Assumption
Plasma storage and handling*		
Area occupied by freezer, €	3,500 (2,800, 4,200)	PC
Amortization of freezer, €	10,315 (8,252, 12,378)	PC
Freezer maintenance, €	6,444 (5,155, 7,732)	PC
Alarm maintenance, €	2,100 (1,680, 2,520)	PC
Alarm calibration, €	457 (365, 548)	PC
Electricity, €	25,200 (20,160, 30,240)	PC
Storage canisters, €	800 (640, 960)	PC
Information system adaptation, €	600 (480, 720)	PC
Technical personnel, €	28,000 (22,400, 33,600)	PC
Calling donors, €	1.5 (1.20, 1.80)	PC
Retesting donors, €	16.5 (13.20, 19.80)	PC
Loss rate, handling MBP	0.010 (0.008, 0.012)	PC
Loss rate, handling QP	0.035 (0.028, 0.042)	PC
Passive quarantine, loss rate because donors do not return	0.450 (0.360, 0.540)	PC
Active quarantine, loss rate because donors do not return	0.300 (0.240, 0.360)	PC
Plasmapheresis loss rate because donors do not return	0.200 (0.160, 0.240)	PC
Loss rate because donors test positive for infectious agent	0.0005 (0.0004, 0.0006)	PC
Per litre value of quarantine plasma for fractionation, €	43 (22, 65)	PC
Per unit cost of MBP treatment, €	22 (17, 26)	PC
Adverse event and breakthrough infection costs, €	**Cost in € (range)**	**Source**
Symptomatic WNV, febrile	7,577 (6,100, 9,100)	Staples *et al*. [25]
Symptomatic WNV, neuroinvasive disease	52,934 (42,300, 63,500)	Staples *et al*. [25]
WNV, sequelae of neuroinvasive disease	23,672 (18,937, 28,400)	Staples *et al*. [25]
CMV retinitis	4,968 (3,874, 5,961)	Keilberger *et al*. [26]
CMV infectious mononucleosis	4,968 (3,874, 5,961)	Keilberger *et al*.[26]
Severe allergy	4,910 (3,928, 5,892)	Kacker *et al*.[27]
Non-severe allergy (utility decrement)	179 (143, 215)	Kacker *et al*.[27]
HCV, acute	4,864 (3,891, 5,836)	Buti *et al*.[28]
HCV, chronic	243 (194, 291)	Buti *et al*.[28]
HCV, compensated cirrhosis	435 (348, 523)	Buti *et al*.[28]
HCV, hepatocellular carcinoma	6,811 (5,449, 8,173)	Buti *et al*.[28]
HBV, acute	871 (697, 1045)	Idris *et al*.[29]
HBV, chronic	259 (208, 311)	Idris *et al*.[29]
HBV, compensated cirrhosis	465 (372, 558)	Idris *et al*.[29]
HBV, hepatocellular carcinoma	7,267 (5,813, 8,720)	Idris *et al*.[29]
Variceal bleeding, year 1	4,967 (3,973, 5,960)	Buti *et al*.[28]
Variceal bleeding, subsequent years	1,511 (1,209, 1,813)	Buti *et al*.[28]
Hepatic encephalopathy, year 1	6,035 (4,827, 7,242)	Buti *et al*.[28]
Hepatic encephalopathy, subsequent years	1,540 (1,232, 1,848)	Buti *et al*.[28]
Ascites, year 1	1,424 (1,139, 1,709)	Buti *et al*.[28]
Ascites, subsequent years	10,854 (8,683, 13,024)	Buti *et al*.[28]
Liver transplant	139,400 (111,500, 167,300)	Buti *et al*.[28]
Post-liver transplant	15,394 (12,315, 18,473)	Buti *et al*.[28]
HIV, acute	-	Assumed untreated
HIV, chronic	9,877 (7,902, 11,853)	López-Bastida *et al*.[30]
AIDS	12,765 (10,212, 15,318)	López-Bastida *et al*.[30]
FNHTR	90.78 (72.62, 108.94)	Kacker *et al*.[27]

*For 8,000 units of plasma. PC: personal communication; QP: quarantine plasma; MBP: methylene blue- and visible light-treated plasma; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; CMV: cytomegalovirus; WNV: West Nile virus; AIDS: acquired immunodeficiency syndrome; FNHTR: febrile non-haemolytic transfusion reaction.

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Spain and an annual incidence of plasma transfusion of 0.0039[14]. We assumed 50-50% market share for MBP and QP.

Cost-utility

Our base case analysis was a comparison of MBP and QP FFP produced from WB with passive and active donor recall. We used cost and QALY estimates to calculate incremental costs and QALY and the incremental cost-effectiveness ratio (ICER) presented as €/QALY gained.

Sensitivity analysis

Univariate sensitivity analyses were conducted for both the budget impact and cost-utility models. We performed univariate sensitivity analyses to determine the impact of all individual model parameters on results. We derived sensitivity ranges from 95% confidence intervals for parameters when available. When these were not available we used ±20% for probabilities and ±50% for costs. When the parameter was assumed or based on experts' opinion, we also used ±50% to represent greater uncertainty, capping probability estimates whose ranges exceeded 0 or 1 at these respective values.

We conducted probabilistic sensitivity analysis to evaluate the overall uncertainty by assigning probability distributions to all parameters in the model. We performed 5,000 second order Monte Carlo simulations and used the net-benefit framework (a linearisation of the ICER based on varying willingness to pay per QALY gained) to compute the probability of cost effectiveness and to construct a cost-effectiveness acceptability curve.

Results

Budget impact

In the passive quarantine scenario, MBP led to a net increase of € 850,352 compared to QP over 5 years, or a net cost increase of approximately € 170,000 per year. In the active quarantine scenario MBP led to net savings of € 5,890,425 compared to QP over 5 years, or approximately € 1,178,000 per year. If the cost of QP is not recovered by selling non-usable FFP for fractionation, MBP is cost saving for all scenarios considered, including WB collections with passive quarantine. For this scenario MBP led to net savings of € 1,503,235 compared to QP over 5 years.

Cost-utility

Results of the baseline cost-utility analysis are summarised in Table III. In both the passive and active quarantine scenarios, on average MBP increased QALY by 0.000010225 compared to QP. Under the passive quarantine scenario, MBP increased mean cost by € 7.21 per patient compared to QP for ICER of € 705,126/QALY gained. In the active quarantine scenario, MBP reduced mean cost by € 50.46 per patient compared to QP and dominated QP i.e., MBP was both more effective and less costly.

Sensitivity analyses

Sensitivity analysis results presented here are restricted to the cost-utility analysis. A tornado diagram of the univariate sensitivity analysis for the passive quarantine scenario is shown in Figure 2 (panel A). The ICER was most sensitive to the cost of MBP processing, the mean yield per donation from WB, the cost per unit of plasma derived from WB collections, the cost per litre of plasma obtained for fractionation, and the estimated number of units produced in a year. Panels B and C of Figure 2 are tornado diagrams of the univariate sensitivity analysis for the active quarantine scenario. Because we estimated that MBP FFP was dominant over QP FFP, we present separately the impact of varying individual parameters on incremental QALY (panel B) and incremental costs (panel C). The incremental QALY were most sensitive to the time in days a patient would have a severe allergic reaction and the incremental cost was most sensitive to the cost of MBP processing.

The results of the probabilistic sensitivity analyses for the passive quarantine scenario are presented in Figure 3 as a scatter plot and cost-effectiveness acceptability curve. As shown in the scatter plot, there is uncertainty as to whether MBP increases costs compared to QP (some simulations indicate increased incremental costs whereas others indicate decreased incremental

Table III - Baseline cost, outcomes and cost-utility analysis comparing MBP to QP from whole blood-derived plasma.

Outcome	Passive quarantine			Active quarantine		
	Quarantine FFP	*MB treated FFP*	*Difference*	*Quarantine FFP*	*MB treated FFP*	*Difference*
Cost	€ 201.85	€ 209.06	€ 7.21	€ 259.52	€ 209.06	€ −50.46
Life years	3.347591921	3.347592727	0.000000805	3.347591921	3.347592727	0.000000805
QALY	3.012823085	3.012833310	0.000010225	3.012823085	3.012833310	0.000010225
Cost per QALY gained			€ 705,126			Dominant*

*Dominant means MBP is more effective and less costly compared to QP. MBP: methylene blue- and visible light-treated plasma; QP: quarantine plasma; FFP: fresh frozen plasma; QALY: quality-adjusted life years.

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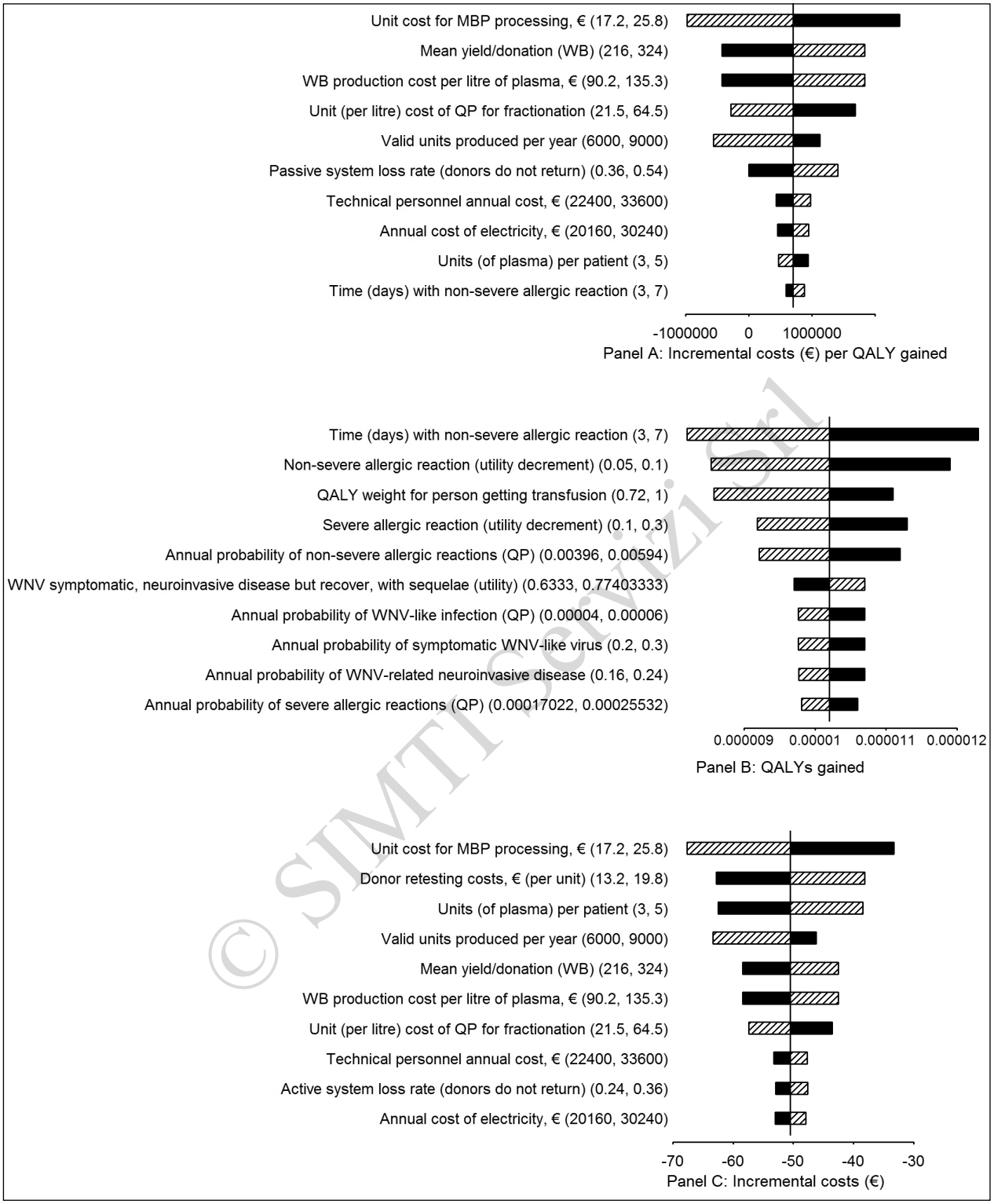

Figure 2 - Tornado diagrams of univariate sensitivity analyses showing the impact of varying parameters through their ranges (i) on the ICER comparing MBP to QP in the passive quarantine scenario (panel A), (ii) on the increase in QALY comparing MBP to QP prepared from whole blood in the active quarantine scenario (panel B) and on the decrease in costs comparing MBP to QP prepared from whole blood in the active quarantine scenario (panel C). The ten most sensitive parameters are shown.
MBP: methylene blue- and visible light-treated plasma; WB: whole blood; QP: quarantine plasma; QALY: quality-adjusted life years; WNV: West Nile virus.

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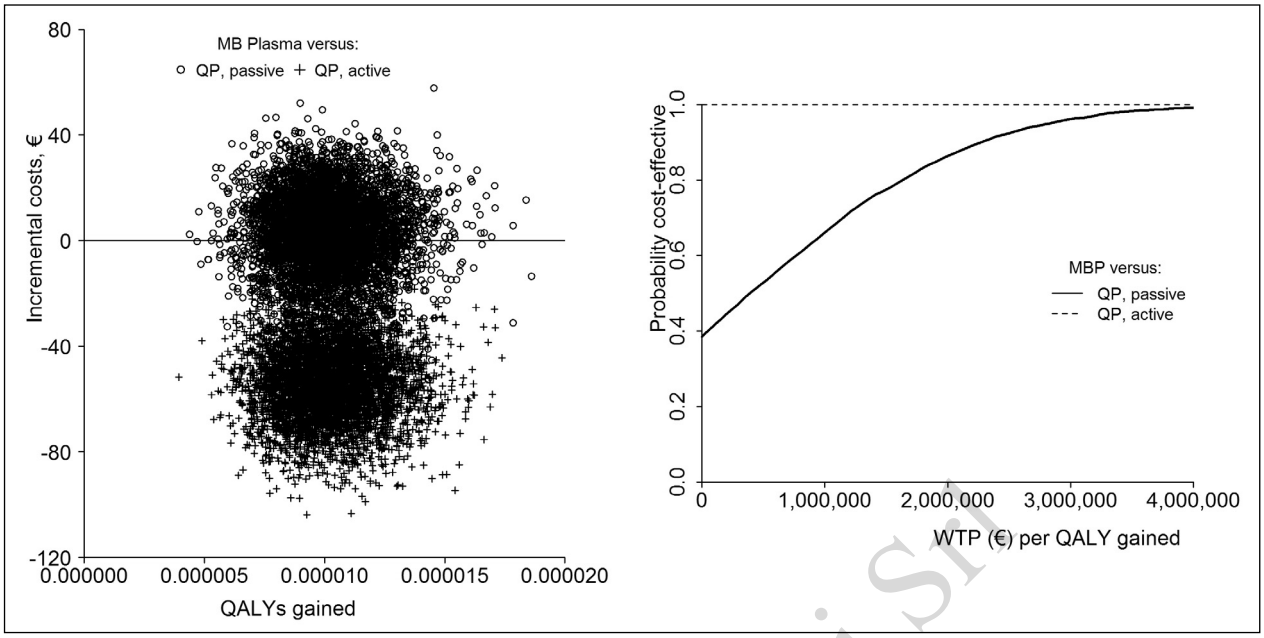

Figure 3 - Probabilistic sensitivity analysis comparing MBP to QP prepared from whole blood under the passive and active quarantine scenarios.
The figure on the left is a scatter plot of incremental cost and QALY gained pairs, and the figure on the right shows a cost-effectiveness acceptability curves For the passive quarantine scenario, the scatter plot shows that MBP is more effective in all 5,000 Monte Carlo simulations, but approximately half of the time the total incremental cost is higher for MBP. For the active quarantine scenario, MBP is more effective and has lower incremental costs in all 5,000 Monte Carlo simulations. The cost-effectiveness acceptability curve indicates the probability of cost-effectiveness at different thresholds of willingness to pay (WTP) for a QALY gained. MBP: methylene blue- and visible light-treated plasma; QP: quarantine plasma; QALY: quality-adjusted life years.

costs) but much greater certainty that MBP, compared to QP, increases QALY. In the cost-effectiveness acceptability curve, at a willingness to pay threshold of € 1,000,000, MBP has a cost-effectiveness probability of 67%. Results of the probabilistic sensitivity analyses for the active quarantine scenario are also shown in the cost-effectiveness scatterplot and cost-effectiveness acceptability curve in Figure 3. The plots show that the dominance of MBP over QP with respect to both costs and effects is robust for this scenario.

Discussion

In this analysis comparing MBP to QP we found that the type of plasma collection approach and quarantine system will influence the budget impact and cost-utility of MBP. If QP is as simple as possible relying on plasma from WB collection and passive quarantine, QP is less costly than MBP, but only if recovered plasma that cannot be transfused from QP is sold for fractionation. If recovered QP is not sold for fractionation the budget impact favours MBP in all scenarios. Without the recovered plasma option for QP, MBP would be more financially favourable, more effective, and represent a dominant strategy over QP. Several other analyses were developed including costs and consequences of collecting apheresis plasma and multicomponent apheresis coupled with passive or active donor recall, but these approaches are used less commonly in Spain and so the results are not reported here. In these analyses, the patterns observed for WB were largely replicated (*data not shown*).

In terms of cost-utility, MBP was estimated to be more effective than QP in all of our analyses, although the gain in QALY was small. As a result, in the WB collection and passive quarantine scenario, the ICER for MBP was high relative to typical acceptable thresholds in health and medicine when recovered QP is sold for fractionation. In the context of blood safety, the ICER result of just over € 700,000/QALY is consistent with that of several other interventions which have been adopted in countries with high development indices[15], including Spain. The cost-utility findings of the use of MBP compared to QP including recovered plasma sold for fractionation are similar to those for other pathogen inactivation technologies focused on the treatment of plasma[16,17]. Nucleic acid testing is commonplace in most countries with high development indices and its cost-utility has been estimated to range between € 1,500,000-€ 6,000,000 per QALY depending on whether mini-pool or individual donation testing is adopted[18,19]. In Spain, individual donation nucleic acid testing is used to screen donations for HIV, HBV, and HCV.

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The cost of treating HCV infection with new drug therapies was not included in this analysis. With individual donation HCV NAT testing in place the residual risk of transmission is very low. If we were to include the cost of new drug therapies in the analysis, the effect would be to improve the relative costs and cost-utility of MBP compared to QP albeit to a small degree because the risk of transfusion-transmitted HCV is very low.

There are limitations to our analyses. Data for Spain were not available for us to use for adverse events after plasma transfusion. For example, Spanish haemovigilance data on adverse events following the transfusion of plasma do not differentiate between QP and MBP. Better-differentiated outcome data could alter our results. We used data from other Mediterranean countries in Europe, which show higher adverse events for QP than for MBP[6,20]. The majority of these events are allergic reactions or FNHTR. The patterns observed in Greece and other countries have been observed in Spain[5], but have not yet been reported in sufficient detail such that Spanish data could be used in our evaluation.

Another limitation is that the QP costs are from one blood centre. Different centres in Spain use different approaches to QP, including passive and active quarantine, and also different approaches to inventory control, such as manual and automated storage and retrieval of plasma units. Each of these approaches to QP will influence the budget impact and cost-effectiveness of the approaches used to increase the safety of plasma transfusions.

A further limitation is that the adverse events associated with plasma transfusion, which have been included in this analysis, do not represent an exhaustive list of all infectious and non-infectious threats. For the majority of known transfusion-transmissible viruses, plasma is the component with the highest risk of transmission while platelets have the highest risk of bacterial contamination and red cells the highest risk of transmission of cell-associated pathogens such as *Plasmodium* (malaria) and *Babesia* (babesiosis). A further aspect of this limitation with respect to the available haemovigilance data is the inclusion of CMV as one of the adverse events associated with FFP. While CMV is a cell-associated virus and, therefore, unlikely to be primarily transmitted by plasma[21], the haemovigilance data from Greece did report the occurrence of plasma-associated CMV transmission. This risk is low and CMV outcomes or costs were not influential parameters in any of our analyses. Even so, the inclusion of CMV in our analysis serves as a surrogate for other viral infections which might have serious consequences on specific populations of patients and for which testing may not be in place, thus establishing a differential risk of transmission between QP and MBP. Any plasma intervention that uses an active reduction or inactivation technology, such as MBP, solvent/detergent treatment, riboflavin plus ultraviolet light, or amotosalen plus ultraviolet light treatment, has increased potential to reduce other viral infections, which QP alone could not prevent. However, the low absolute risk of adverse events, both infectious and immunological, associated with plasma infusion, may explain the lack of randomised controlled trials directly comparing the safety of FFP prepared using different technologies[22]. If additional but other uncommon infections were included, the overall estimate of better effectiveness for using MBP compared to QP would be expected to increase. Finally, the reduction of infectious risk is counter-balanced by the risks related to the inactivation technology or specific reactants, which are inherent in the process of each inactivation procedure[23]. On balance, these non-infectious immunological adverse effects are minimal and have been shown to be lower for MBP than for QP.

Conclusions

In many countries in Europe the decision to use pathogen reduction technology has not been driven by the results of cost-utility analyses because the thresholds that are commonly regarded as cost-effective in clinical practice have not been met by most blood safety interventions, at least in countries in which as close to zero-risk for infectious threats has been perceived as the most appropriate blood safety policy[24]. Health economics involves two considerations: the overall impact on health care budgets and value for money spent. The budget impact for MBP varied according to the approach used to obtain FFP and the quarantine system in use for plasma. Although the full cost of QP is difficult to calculate and dependent on the structure of the QP system, when costs previously unaccounted for are included, MBP approaches cost neutrality for WB and is cost-saving and more cost-effective under any active QP and/or apheresis approach. Finally, the analysis of MBP shows that this technology is more effective than QP in terms of generating additional health benefit for plasma-transfused patients, regardless of the quarantine system in place.

Funding and resources

This study was funded by an unrestricted grant from Macopharma.

Authorship contributions

BC conceived the study. JBB, SJL, and BC designed the study, including the development of the economic models. JBB, SJL, EC, and BC obtained data and performed the analysis. JBB wrote the first draft of the manuscript. SJL, EC, and BC each wrote sections of the final manuscript. All Authors approved the final submission version of the manuscript.

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The Authors declare no conflicts of interest.

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Arrived: 16 May 2016 - Revision accepted: 30 August 2016
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