資料２－１

Ａ　研究報告（概要一覧表）

平成２５年１０月２日
（平成２５年５月～平成２５年７月受理分）

研究報告のまとめ方について

１　平成２５年５月１日～平成２５年７月３０日までに提出された感染症定期報告に含まれる研究報告（論文等）について、重複している分を除いた報告概要一覧表を作成した。

２　一覧表の後に、個別の研究報告の詳細を添付した。

感染症定期報告の報告状況（2013/5/1～2013/7/31）

【血液製剤、輸血の安全性に関する報告】

血対課	感染症（PT）	出典	概要	新規文献番号
＜肝炎ウイルス＞				
1E+05	E型肝炎	Vox Sang 103(2012):184	米国におけるE型肝炎ウイルス（HEV）のプール血漿を介した感染の報告。2001年から2003年までの間にプール血漿を大量投与された血栓性血小板減少性紫斑病患者38例を対象にレトロスペクティブに調査を実施した。38例のうち17例はSD（solvent detergent）処理血漿で、19例はクリオ上清血漿で治療を受けていた。SD処理血漿で治療を受けたうち、4例において治療6カ月後に抗HEV IgGが陽転し、そのうちの2例では抗HEV IgMの陽転も認められた。一方、クリオ上清血漿で治療を受けた19例では血清学的にHEV感染は認められなかった。これはプール血漿によるHEV感染を示唆する抄録であり、更なる調査が必要である。	1
＜その他のウイルス＞				
1E+05	パルボウイルス感染	Pediatr Infect Dis J. 32(2013):178-179	ヒトボカウイルス（HBoV）に関する総説。2005年に呼吸器感染症の患児から未知のDNAウイルスが検出され、分析の結果、ウシ及びイヌのパルボウイルスと類似したウイルスが同定され、HBoV1と命名された。これまでに3種類の新たなHBoVが同定されている（HBoV2～4）。HBoVはパルボウイルス同様、エンベロープをもたない微小なDNAウイルスであり、5kbの直鎖一本鎖DNAを有する。HBoV1は呼吸器及び血清から検出され、HBoV2～4は主に糞便から検出される。呼吸器感染症に罹患している低年齢の小児において、HBoV1のDNAの保有率は10～33%である。糞便検体におけるHBoV2の検出率は小児で26%（成人では4%）であるが、HBoV3及び4の検出率は小児・成人ともに5%未満である。これまでに、HBoV1と上下気道感染症を関連付ける十分なデータが得られ、HBoV2と胃腸炎を関連付けるいくつかのデータが得られている。	2
1E+05	鳥インフルエンザ	http://www.who.int/influenza/human_animal_interface/influenza_h7n9/RiskAssessment_H7N9_07Jun13.pdf	中国における鳥インフルエンザA（H7N9）型（以下、H7N9）感染の報告。2013年6月7日時点で、WHOへ報告されたH7N9感染症例は合計132例である。既に37例の感染者が死亡し、他の感染者についても症状は重篤である。感染源や感染経路については調査が進められているが、これまでの情報からは、生鮮市場の家禽からヒトへ感染したと推察されている。H7N9感染者の小規模なヒト-ヒト感染は4件確認されているが、継続的なヒト-ヒト感染は確認されていない。H7N9感染者と接触した2000名以上を対象にモニタリング及び検査が実施されたが、H7N9感染例は少数確認されたのみであった。WHOは関係国に対して状況の監視を継続するよう求めている。	3
1E+05	鳥インフルエンザ	WHO/GAR April 1, 2013	中国における鳥インフルエンザA（H7N9）型（以下、H7N9）感染の報告。中国国家衛生・計画出産委員会は、2013年3月31日、WHOに対してH7N9のヒト感染症例3例を報告した。これらの症例は、中国疾病予防管理センターによる検査で3月29日に感染が確定した。患者は上海で2例、安徽省で1例が確認され、2月19日から3月5日までの間に、呼吸困難を伴う重症の肺炎を発症した。2例は死亡し、1例は現在重篤な状態である。患者の間に疫学的関連は認められておらず、感染源及び感染経路の調査が進められている。	4
1E+05	ウイルス感染	ProMED-mail 20130215.1544940	英国における新型コロナウイルス（NCoV）感染の報告。2013年2月15日、英国健康保護局（HPA）は、NCoV感染が既に確定している患者の家族内に新たにNCoV感染が確認されたことを発表した。この家族内におけるNCoV感染者はこれで3例目である。この患者は、英国在住者で、最近の海外渡航歴はない。HPA担当者によると、本事例はヒト-ヒト感染によるものとみられるが、通常の接触による感染リスクは依然低いと考えられている。HPAは国内外の関係機関と協力しながら、医療従事者や国民に対して最新の情報を提供することとしている。	5
1E+05	ウイルス感染	Int J Infect Dis. 17(2013):e206-e208	中国において重症熱性血小板減少症候群（SFTS）がヒトからヒトへ感染した事例の報告。湖北省の63歳の発端患者は、2012年5月6日、発熱、血小板減少及び白血球減少の臨床症状を示し、5月12日に死亡した。この患者は典型的なSFTSの臨床症状を示したものの、SFTSの診断はなされなかった。発端患者の死後、その血液や血性分泌物に触れた2名、並びに血まみれの服をきれいにするのを手伝った1名が、曝露から7-12日に発熱、血小板減少及び白血球減少を含む臨床症状を発症した。3名は、RT-PCR法及びウイルス分離によりSFTSと診断された。発端患者の発症から死後までに曝露された他の58名については、患者の分泌物に直接触れておらず発症した者はいない。以上より、SFTSウイルスは患者の死体血液や血性分泌物との接触を介して、ヒトからヒトへ感染することができると結論付けられた。	6

1E+05	ウイルス感染	WHO/GAR May 17, 2013	中東及び欧州で流行する新規コロナウイルス（NCoV）に関する報告。2012年4月から2013年5月10日までの間に、中東諸国及び欧州3カ国（仏、独及び英）で確認されたNCoV感染例は計40例である。2013年4月6日以降、サウジアラビアAl-Ahsa地区において21例のNCoV感染が新たに確認され、この中には家族内で伝播したケースや感染者と接触した後に発症したケースなどが含まれていた。このアウトブレイクの感染源については現在調査中である。また、フランスにおいて、ドバイからの帰国後にNCoV感染が確認された症例と病室をともにしていた症例1例でNCoV感染が確認された。NCoVのヒト-ヒト感染は、これまで医療機関内や家族内において確認されているが、コミュニティ内で継続的に感染拡大する可能性があるか、関係者は関心を寄せている。	7
1E+05	ウイルス感染	Eurosurveillance. 18(2013):1-7	中東で流行する新規コロナウイルス（MERS-CoV）の感染拡大のシナリオに関する報告。2013年5月30日時点でMERS-CoVの感染者は全世界で50例が確定しており、30例が死亡している（死亡率60%）。感染源や感染経路に関しては不明であり、宿主動物についても特定されていないが、ヒト-ヒト感染の事例が確認されている。本報告では、ヒト-ヒト感染の起こりやすさの大小に応じて大きく3通りの感染拡大のシナリオが想定されることを示し、必要となる疫学的調査や流行抑止策について提案している。	8
1E+05	ウイルス感染	http://www.who.int/csr/disease/coronavirus_infections/update_20130709/en/index.html	中東で流行する新規コロナウイルス（MERS-CoV）感染に関する報告。2013年7月9日時点でMERS-CoVの感染確定例は全世界で80例が報告されており、45例が死亡している（死亡率は56%）。ヒト-ヒト感染の事例が確認されているが、継続的なヒト-ヒト感染による感染拡大は認められていない。しかし、今回新たに報告された16例のMERS-CoV感染確定例のうち、8例は無症候性の感染者であった。これは、他にも報告されていないMERS-CoV感染者が存在している可能性を示しており、既に継続的なヒト-ヒト感染が起きている可能性も示唆している。継続したモニタリングと徹底した疫学的分析が求められる。	9
1E+05	ウイルス感染	Transbound Emerg Dis. 60(2013):193-196	中国におけるテンブスウイルス（TMUV）感染の報告。中国では、アヒル、ガチョウ及びイエスズメのTMUV感染が報告されている。今回、ヒトにおけるTMUV感染について調査した。山東省においてアヒルを扱う業務の従事者から採取された血清サンプル132本のうち、95本（71.9%）が抗TMUV抗体陽性であり、63本（47.7%）がTMUVのRNA陽性であった。アヒルの産卵低下に関連することが知られている遺伝子について、今回分離されたTMUVはアヒル由来TMUVと95.5%の相同性を示した。これらの結果は、中国においてTMUVが人獣共通感染症として見落とされてきた可能性があることを示唆している。	10
＜クロイトフェルト・ヤコブ病＞				
1E+05	異型クロイツフェルト・ヤコブ病	http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/ucm339920.htm	米国における変異型クロイツフェルト・ヤコブ病（vCJD）の感染リスクに関する予備的評価。食品医薬品局（FDA）は、米国での赤血球製剤輸血を介したvCJD感染の確率を推定するためリスク評価を実施した。英国におけるvCJDの想定有病率が低い（100万人当たり約1.7人の感染）又は高い（100万人当たり約493人の感染）場合の2通りを仮定した。その結果、赤血球製剤 1単位の輸血による予測リスクは、想定有病率を高く仮定した場合に48万分の1であり、低く仮定した場合に134万分の1であった。FDAは、リスク評価の手法やリスクに対する解釈が妥当であるかについて、伝達性海綿状脳症諮問委員会に助言を求めている。	11
1E+05	クロイトフェルト・ヤコブ病	http://ansm.sante.fr/S-informer/Informations-de-securite-Retraits-de-lots-et-de-produits/Medicaments-Derives-du-Sang-LFB-Biomedicaments-Rappel-de-lots2	フランスにおける弧発性クロイツフェルト・ヤコブ病（CJD）に起因するアルブミン製剤の回収の報告。LFB Biomedicament社は、仏医薬品・保健製品安全庁との合意のもと、弧発性CJDを発症した可能性のある患者の血漿から製造されたアルブミン製剤Vialebexの2ロットの回収を実施した。この回収は予防的措置であり、本件によるCJDの感染の報告はない。当該製剤の製造工程においては、プリオン除去に効果のある処理が含まれている。血液製剤によるCJD感染は理論上のリスクではあるが、証明され、特定されたリスクではないとされている。	12

＜その他＞				
1E+05	バベシア症	Transfusion 2013 Feb 27. [Article in press]	米国における*Babesia microti*の陽性率に関する報告。コネチカット州において2009年8月から10月までに供血者から採取された血液サンプルを対象に、リアルタイムPCRにより*B. microti*のDNAの陽性率を調べ、同時に蛍光抗体検査（IFA）の結果と比較した。対象となった1,002例の供血者のうち25例（2.5%）がIFA陽性であり、3例（0.3%）がPCR陽性であった。PCR陽性の3例のうち、1例はIFA陰性であり、ウィンドウ期であった可能性が考えられた。この結果は、*B. microti*を媒介するダニが増える時期においては、ウィンドウ期の感染を検出する核酸検査を含めた検査アルゴリズムが必要であることを示している。	13
1E+05	リケッチア症	Clin Infect Dis. 56(2013):e105-e107	輸血によるエールリッヒア症伝播の可能性に関する報告。2011年夏、ジョージア州の9歳の小児が発熱、疲労、不安感、嘔吐、下痢及び点状出血発疹の症状を呈し、検査の結果、エールリッヒア症と診断された。患児は急性リンパ性白血病のため屋外で活動することはなく、家族によればダニから感染する可能性は思いつかないとのことであった。発症の前に複数回の輸血を受けていたことから、輸血による感染の可能性があるとして調査が行われたところ、輸血製剤のドナーのうちの1人が*Ehrlichia*種に対する抗体を保有していた。当該ドナー由来の血液製剤を投与された8名の患者のうち、3名はエールリッヒア症とは無関係な原因で死亡しており、残る5名はエールリッヒア症の検査は陰性であった。本事例に関連する血液製剤はすべて白血球除去及び放射線照射の処理を受けており、今回の報告は、こうした血液製剤がリケッチア症の感染源となる可能性を示した初めての報告である。	14
1E+05	梅毒	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM340993.pdf	米国食品医薬品局（FDA）は、全血又は血液成分（原料血漿を含む。）を採取する施設に対する、梅毒のスクリーニング試験に基づいたドナーのスクリーニング及びその試験法、並びにドナーの管理に関する勧告事項を改訂し、ドラフトガイダンスとして公表した。このドラフトガイダンスは、2003年6月付けの「梅毒のスクリーニング試験に基づいたドナーと製品の管理のための勧告事項（改訂版）」と換わるものとなり、問診における梅毒の病歴を有するドナーの同定方法、及び梅毒のスクリーニング試験（トレポーマ試験あるいは非トレポーマ試験）に基づくドナースクリーニング方法が示されている。また、本ドラフトが最終版となった場合には、1991年12月付けのメモランダム「梅毒試験の結果に基づくドナーの不適格判定と製品の出荷に関するFDA勧告事項の説明」と換わるものとなる。	15
1E+05	感染	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/UCM341088.pdf	米国食品医薬品局（FDA）は、原料血漿ドナーのスクリーニングに用いる病歴問診票及び付属資料（以下、SPDHQ文書）についてガイダンスを公表した。ガイダンスには以下の点が含まれる。①FDAは、血漿タンパク質製剤協会が作成したSPDHQ文書について、FDAの要件及び勧告に則るものであると認める。②FDAは、すべての許可予定のSPDHQ文書をウェブサイトで公開する予定である（http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/ucm255235.htm）。これらのSPDHQ文書は、ドナー適格者の病歴情報を得るための手段を提供するものとして、FDAが認めたものである。③公開予定のSPDHQ文書に基づいて原料血漿製造業者が製法変更を行う場合のFDAへの報告方法について提示する。 （SPDHQ文書は、米国血漿蛋白製剤協会が作成にたものであり、ドナーの病歴（HIV、肝炎等）や健康状態等に関する問診票、当該問診票使用の手引き、ドナー教育用ポスター（リスク基準、血液感染症の流行地域）から構成される。）	16

感染症定期報告の報告状況（2013/5/1～2013/7/31）

血対課ID	受理日	番号	報告者名	一般名	生物由来成分名	原材料名	原産国	含有区分	文献	症例	適正措置報告
130095	22-Jul-13	130315	CSL ベーリング株式会社	乾燥濃縮人C1－インアクチベーター	人C1-インアクチベーター	人血液	米国、ドイツ、オーストリア	有効成分	あり	あり	なし

Ｂ　個別症例報告概要

○ 総括一覧表
○ 報告リスト

平成２５年１０月２日
（平成２５年５月～平成２５年７月受理分）

個別症例報告のまとめ方について

個別症例報告が添付されているもののうち、個別症例報告の重複を除いたものを一覧表の後に添付した（国内症例については、資料３において集積報告を行っているため、添付していない）。

資料２－２

Ａ　研究報告（詳細版）

平成２５年１０月２日
（平成２５年５月～平成２５年７月受理分）

別紙様式第 2-1
番号 11

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2013 年 03 月 25 日	新医薬品等の区分 該当なし	厚生労働省処理欄

一般的名称	乾燥濃縮人アンチトロンビンⅢ	研究報告の公表状況	Vox Sanguinis 2012; 103(July): 184-184	公表国 アメリカ
販売名 (企業名)	①ノイアート静注用 500 単位　(日本血液製剤機構) ②ノイアート静注用 1500 単位　(日本血液製剤機構)			

研究報告の概要

プール血漿を介したＥ型肝炎ウイルス（HEV）のもっともらしい感染の血清学的及び分子的根拠

背　　景：
Ｅ型肝炎ウイルス(HEV)感染は通常糞口及び食品媒介経路で発生するが、近年では血液の安全性への潜在的リスクとして再び現れている。輸血感染 HEV の 6 つの報告症例がある；日本の 3 症例、サウジアラビア、英国及びフランスの各 1 症例。献血者での HEV RNA の陽性率は、日本と英国の 0.01%からインドのプネーの 1.5%まで変化する。HEV RNA は血漿プールでも発見され、範囲が未定義のままである輸血安全性へのリスクをもたらす可能性がある。一般に感染性微生物の除去のために使われる有機溶媒/界面活性剤(SD)処理工程は、熱や化学的に最も耐性な病原体の一つである HEV の様なノンエンベロープウイルスの不活性化に効果的でない。

目　　的：
血漿プールを介した HEV 感染の可能性を評価するために、プール血漿を大量に投与された血栓性血小板減少性紫斑病(TTP)の患者でレトロスペクティブな調査を行った。

方　　法：
患者は 2001 年から 2003 年の間に調査に登録された；彼らは SD 処理血漿（SDP）、或いはクリオ上清血漿（CSP）の何れかで治療を受けた。SDP プールは 2,500 人の米国のドナー（マサチューセッツ州ウオータータウンの VITEX）から、そして CSP プールはカナダのドナーから製造された。3 検体は治療後 0、1 及び 6 ヶ月時に TTP 患者から採取し、-20℃で凍結保存した。推定される HEV 感染の血清学的及び分子追跡は、MP Diagnostics HEV ELISA キット及び RealStar RealStar HEV RT-PCR キット、そして/または nested RT-PCR で行った。配列決定は標準技術を用いて ABI 3730 シーケンサーで行った。

結　　果：
血漿交換療法(20-40L の血漿/患者)を受けた 38 人の TTP 患者で行った;17 人は SDP を、19 人は CSP を、そして 2 人は新鮮凍結血漿と Pentaspan、或いはアルブミンの治療を受けた。患者の誰一人として 6 ヶ月間の観察期間の間、ウイルス性肝炎の臨床的徴候を示さなかった。38 人の患者全員は、治療後 0、1 ヶ月時に HEV 感染の血清学的証拠はなかった。しかし、SDP の治療を受けた 17 人の患者の内 4 人は、抗 HEV IgG が 6 ヶ月後に陽転した、そして彼らの 2 人は抗 HEV IgM も陽性になった。4 人の患者全員は 6 ヶ月時に HEV RNA は陰性であったが、抗 HEV IgG と IgM の両方が陽転した 2 人の患者の治療後 1 ヶ月の検体は HEV RNA が陽性であった；一人は RT-PCR による、そして二人目は nested RT-PCR による；後者からの増幅産物の塩基配列決定により遺伝子型 3 に分類された、そして系統樹再構築のために最尤法を用いた系統樹再解析により分離された株は米国産ブタＨＥＶ分離株にもっとも近縁であった。CSP 治療を受けた 19 人の患者は、誰も血清学的に HEV 感染の根拠を示さなかった。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-1 抗体陰性で、かつ ALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人アンチトロンビンⅢを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

文献番号 1

医薬品
医薬部外品　　研究報告　調査報告書
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結　　論：
HEV 感染に関する血漿プールの安全性は現時点では高いと考えられているが、包括的な方法で調査されていない。この報告書は、プール血漿による HEV 感染の最初の間接的な根拠を示し、さらなる調査を必要とする。

報告企業の意見	今後の対応
E型肝炎ウイルス（Hepatitis E virus：HEV）は直径27～38nmの球状粒子で、エンベロープはなく、長さ約7,300塩基対の一本鎖RNAを内包している。万一、原料血漿にHEVが混入したとしても、Murine encephalomyocarditis virus（EMC）及びCanine parvovirus（CPV）をモデルウイルスとしたウイルスクリアランス試験成績から、本剤の製造工程において不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。

Methods: Using a Transmissible Spongiform Encephalopathy (TSE) sheep model, we characterized the abilities of whole blood, RBC, plasma and buffy-coat prepared from preclinical infected animals to transmit the disease through the transfusion route. Blood components from infected sheep whole blood were prepared following the same processes as those used in human transfusion medicine. We then measured the impact of a standard LD filter and of two different LD/PR prototype filters on the disease transmission rate caused by RBC transfusion. Finally, in the whole blood titration experiment, 200 – 20 – 2 – 0.2 ml of infected whole blood were transfused to free recipient sheep.
Results: In this TSE sheep model, 0.2 ml of whole blood were sufficient to transmit the disease by the transfusion route. Whereas whole-blood, buffy-coat and RBC transmitted the disease with a 100% efficiency, intra-venous administration of crude plasma resulted in an inconsistent infection of the recipients. Only three out the five sheep that received plasma developed the disease and one out five sheep after transfusion with LD-plasma. None of the sheep (n = 15) transfused with LD and LD/PR filtered RBCs developed clinical disease. However in two of these recipient sheep, post-mortem analysis revealed the presence of abnormal prion protein in lymphoid tissues and/or in central nervous system. Despite their high efficacy, LD and LD/PR filters did not provide absolute protection from infection. Nevertheless, LD and LD/PR filtered RBCs prepared from 400 ml of blood were shown to be less infectious than 0.2 ml of whole blood.
Conclusions: Our results support the view that leucodepletion is an efficient, whereas not a 100% optimal, method to reduce the TSE transmission risk by both RBCs and plasma. It also suggests that Prion-reduction filters might not bring clear additional beneficial effect.

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CORRELATION BETWEEN THE LEVELS OF WNV VIRAL LOAD, MODULATION OF CYTOKINES/CHEMOKINES AND CLINICAL DISEASE IN WNV+ BLOOD DONORS

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Background: West Nile virus (WNV) infection is often asymptomatic but a broad range of symptoms can develop, from flu-like symptoms to more serious and sometimes fatal neurological disorders. Ongoing studies are trying to understand the host-virus dynamics that lead to the development of severe symptoms.
Aims: The present study investigated the correlation between the levels of WNV viral load (WNV-VL) and the levels of cytokines/chemokines in plasma and compared their levels in subjects with different clinical disease outcome.
Methods: We built a repository of samples collected from 43 WNV-positive blood donors at 10 time-points after WNV-positive donation. Whole blood and plasma samples collected one, three, and 6 weeks post-donation were characterized for WNV-VL by real-time RT-PCR. Plasma samples were characterized for 52 cytokines/chemokines by multiplex assay. Symptom data derived from two questionnaires inquiring about the development of 12 symptoms over a 3 week period around initial donation allowed for classification of subjects reporting ≥4 symptoms as symptomatic (n = 20) and the others as asymptomatic (n = 21). A generalized linear model with repeated measures (Proc genmod (GEE) SAS 9.2) was used to compare cytokine/chemokine levels on the day of donation and at one, three, and 6 weeks post donation between asymptomatic and symptomatic sub-groups. WNV-VL was correlated to levels of cytokines/chemokines measured at one, three, and 6 weeks post-donation. P-values were converted into FDR using the Multitest SAS procedure.
Results: In WNV+ subjects, TNF-α and IP-10 levels positively correlated with WNV-VL in plasma (estimated difference in slopes, 0.02 and 0.07, respectively, P-values <0.01 and FDRs < 0.03). A negative correlation was found between the levels of IFN-γ, IL-1β, and IL-4 and the levels of VL in plasma (estimated difference in slopes, −0.05, −0.05, and −0.06, respectively, P-values <0.001, and FDRs < 0.01) and between the levels of IL-1β and the levels of VL in whole blood (estimated difference in slopes = −0.06, P-value <0.0001, and FDR = 0.001). Symptomatic subjects had higher levels of EGF, FGF-2, G-CSF, IL-17, MDC, TNF-α, and sIL-2Rα and lower levels of IL-6 than asymptomatic subjects (GEE P-values <0.05 with FDRs < 0.1).
Summary/Conclusion: The data revealed distinct timing for the induction of different cytokines/chemokines after WNV infection. While TNF-α and IP-10 are induced earlier in the ramp-up phase of viremia, others including IFN-γ, IL-1β, and IL-4 are induced later as viral load decreases. The correlation between these cytokines/chemokines and WNV viral load demonstrates the timing of the engagement of the immune response to control the virus. Notably, a higher degree of inflammation was observed in symptomatic than in asymptomatic subjects during the acute phase of WNV infection.

JBPO 2013-006

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SEROLOGIC AND MOLECULAR EVIDENCE OF A PLAUSIBLE TRANSMISSION OF HEPATITIS E VIRUS (HEV) THROUGH POOLED PLASMA

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Background: Hepatitis E virus (HEV) transmission usually occurs by fecal-oral and food-borne routes, however in recent years it is re-emerging as a potential risk to blood safety. There are six documented cases of transfusion-transmitted HEV: three in Japan and one each in Saudi Arabia, United Kingdom and France. HEV RNA prevalence in blood donors varies from 0.01% in Japan and United Kingdom to 1.5% in Pune, India. HEV RNA is also found in plasma pools and may pose a risk to transfusion safety the extent of which remains undefined. Solvent detergent processes, commonly used for reduction of microorganisms, are not as effective for inactivation of non-enveloped viruses such as HEV which is among the most heat and chemically resistant pathogens.
Aim: To evaluate the potential of HEV transmission through plasma pools a retrospective investigation was conducted among patients with thrombotic thrombocytopenic purpura (TTP) treated with large volumes of pooled plasma.
Methods: The patients were enrolled in the study between 2001 and 2003; they received either solvent detergent treated plasma (SDP) or cryosupernatant plasma (CSP). Each SDP pool was prepared from 2500 US donors, (VITEX, Watertown, MA) and CSP pools made from 150 Canadian donors. Three samples were collected from TTP patients at time 0, 1 and 6 months post-treatment and kept frozen at −20°C. Serologic and molecular tracing of presumptive HEV infection was carried out by MP Diagnostics HEV ELISA kit (former Genelabs, Singapore) and RealStar HEV RT-PCR kit (altona-Diagnostics, Hamburg, Germany) and/or nested RT-PCR. Sequencing was performed on an ABI 3730 sequencer using standard techniques.
Results: Thirty-eight TTP patients received plasma exchange treatment (20–40 l of plasma per patient); seventeen received SD-plasma, nineteen were treated with cryosupernatant plasma and two with fresh frozen plasma and Pentaspan or albumin. None of the patients demonstrated any clinical signs of viral hepatitis during the 6-month period of observation. All 38 patients had no serological evidence for HEV infection at 0 and 1 month post-treatment. However four out of seventeen patients treated with SD-plasma seroconverted at 6 months for anti-HEV IgG and two of them were also positive for anti-HEV IgM. At 6 months all four patients were negative for HEV RNA, however the 1 month post-treatment sample from the two patients who seroconverted both for anti-HEV IgG and IgM was positive for HEV RNA; one by real-time PCR and the second by nested RT-PCR; sequencing of the amplified product from the later classified it within genotype 3 and based on a phylogenetic analysis using maximum likelihood method for reconstructing tree topology its closest neighbour is an US swine HEV isolate. None of the 19 patients treated with cryosupernatant plasma showed any serological evidence of HEV infection.
Conclusion: The safety of plasma pools with respect to HEV transmission is considered to be high at the moment, although it has not been investigated in a comprehensive manner. This report provides for the first time indirect evidence of HEV transmission by pooled plasma and warrants further studies.

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AN EVIDENCE-BASED EVALUATION OF THE RISK POSED BY ROSS RIVER VIRUS TO THE SAFETY OF THE AUSTRALIAN BLOOD SUPPLY

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Background: Ross River Virus (RRV) is the most common mosquito-transmitted virus in Australia. Increased rainfall is associated with higher infection rates; both of these were reported in regions of Australia between January and March, 2011. RRV is a blood-borne virus and asymptomatic infections are common, suggesting that transfusion-transmission of RRV is theoretically possible, although not yet recorded. The Australian Red Cross Blood Service (Blood Service) manages the potential risk of RRV transfusion-transmission by: restricting donations from donors diagnosed with RRV for 2 weeks following symptom recovery; an additional 12 month restriction to plasma for fractionation only following symptom recovery; and also blood component quarantine or recall for donors reporting any illness within 7 days of donation. Previous Blood Service risk modelling estimated the theoretical risk of RRV transfusion-transmission by blood based on notified clinical cases in the range of 1 in 4700 to 1 in 47,000. No recent studies have utilized direct testing of blood donors to determine the infection incidence in this population to assess the theoretical risk to the Australian Blood Supply.

医薬品 研究報告 調査報告書

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販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社) 解凍赤血球液-LR「日赤」(日本赤十字社) 照射解凍赤血球液-LR「日赤」(日本赤十字社)		Peltola V, Söderlund-Venermo M, Jartti T. Pediatr Infect Dis J. 2013 Feb;32(2):178-9. doi: 10.1097/INF.0b013e31827fef67.	フィンランド

研究報告の概要

○ヒトボカウイルス感染
2005年、呼吸器感染症の小児の鼻咽頭検体から未知のDNAウイルスが検出された。遺伝子配列分析の結果、ウシ及びイヌ微小パルボウイルスとの類似点が示され、ヒトボカウイルス(HBoV)と命名された。その後、3種類の新たなHBoVも発見されている(HBoV2-4)。
HBoV1は呼吸器から最も検出されるほか、血清からも検出される。一方、HBoV2-4は主に糞便から検出される。世界的に呼吸器感染症に罹患している低年齢の小児において、HBoV1 DNAの保有率は約10%～33%である。腸内のボカウイルスでは、HBoV2の陽性率が最も高く、小児の糞便検体の26%、成人の4%から検出されるが、HBoV3、4の検出率は5%未満である。
これまでの研究から、HBoV1と上下気道感染症を関連付ける十分なデータ、HBoV2と胃腸炎を関連付けるいくつかのデータが得られている。
しかしながらHBoV1が引き起こす疾患負荷については未だ不明な点が多い。また、HBoV1感染の診断には臨床的アプローチ及びPCRと血清学的検査を組み合わせた検査が必要である。

報告企業の意見	今後の対応
2005年に呼吸器感染患児の鼻咽頭検体から初めて検出されたヒトボカウイルスの概論である。	今後も引き続き情報の収集に努める。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-LR「日赤」
解凍赤血球液-LR「日赤」
照射解凍赤血球液-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

文献番号 2

ESPID REPORTS AND REVIEWS

Human Bocavirus Infections

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In 2005, a previously unknown DNA virus was identified in nasopharyngeal specimens from children with respiratory tract infection.[1] Researchers used random polymerase chain reaction (PCR) amplification and high-throughput sequencing methods specifically developed for detection of unknown viral sequences. Analysis of the recovered gene sequences showed resemblance to bovine and canine minute parvoviruses, and the virus was named human bocavirus (HBoV). Later, 3 other HBoV were identified in stool and named HBoV 2, 3 and 4.[2,3] Disease associations of HBoV are not entirely clear, but recent studies provide evidence that HBoV1 causes pneumonia and other respiratory tract diseases, in particular during primary infections.[4]

VIRUS STRUCTURE AND BIOLOGICAL PROPERTIES

HBoV is a small DNA virus with a nonenveloped icosahedral capsid similar to other *Parvoviridae*.[5] The 5kb linear and single-stranded genome is organized in 3 open reading frames that encode 2 forms of the nonstructural protein NS1, a nuclear phosphoprotein NP1, and 2 structural capsid proteins, VP1 and VP2.[6] HBoV types 2–4 have similar genomic organizations as HBoV1 and 10%–30% sequence dissimilarities.[3]

Replication mechanisms of HBoV and the pathogenesis of HBoV infections are poorly characterized. This is largely because no animal model is available and tissue culture of HBoV is difficult, although it has been cultured in primary respiratory epithelial cells.[7] The primary replication site of HBoV1 appears to be the respiratory tract, where it has been detected most frequently and in highest copy numbers. HBoV1 can be found also in serum, pointing to a systemic spread.[8,9] Viral copy numbers of HBoV1 in stool are low. On the contrary, HBoV types 2–4 have been detected predominantly in stool, but the host cell types are not known.[2,3,10]

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HBoV1 has been detected for up to 6 months in serial nasopharyngeal samples.[11,12] Prolonged replication or passive persistence may account for the frequent presence of HBoV1 in asymptomatic children. HBoV1 often is present in samples together with another respiratory virus, which might suggest reactivation of a latent virus by a superinfection. However, there is no documented evidence of establishment of a persistent, latent state by the HBoV.

EPIDEMIOLOGY

Globally the prevalence of HBoV1 DNA in young children with respiratory tract infections is around 10%, in some studies up to 33%.[4] It occurs year-round, but most commonly in the winter. HBoV1 is more frequently detected in young children (<2 years of age) than in older children or adults. Limited knowledge of transmission, persistence, establishment of latency, reinfections and reactivations cause uncertainties regarding the epidemiology of HBoV1. Of the enteric bocavirus types, HBoV2 is the most prevalent with detection rates of up to 26% in stool samples from children, and 4% from adults.[2,3] DNA of HBoV3 and HBoV4 has been detected in <5% of stool samples.

Seroepidemiologic studies have documented that most children have IgG antibodies against HBoV1 by school age.[13,14] Differentiation between seroresponses against HBoV types 1 to 4 is, however, difficult because of cross-reactivity.[15]

CLINICAL MANIFESTATIONS

Many studies have reported an association between a respiratory tract infection and HBoV1 detected by PCR in the nasopharynx. Clinical manifestations have ranged from mild upper respiratory tract infections to severe pneumonia. However, because of insufficient diagnostic methods, selected patient populations and lack of control groups, the majority of studies are of limited value. The pathogenic role of HBoV1 has been challenged by documentation of other viruses in the same samples (up to 90%) and detection of bocavirus also in asymptomatic individuals (up to 44%).[4] In a study of children in day-care centers, 33% of those with respiratory symptoms and 44% of those without symptoms were positive for HBoV1 DNA.[11] Furthermore, 70% of the HBoV1 DNA positive children with symptoms were positive also for another respiratory virus, most commonly human rhinovirus. The mere presence of HBoV1 DNA in the nasopharynx is, therefore, not a sufficient evidence of an acute HBoV1 infection and cannot be used for estimating the clinical impact of this virus. Recently, more solid data for the case that HBoV1 can cause disease have been provided by use of PCR in serum and by serology. In a study of wheezing children, 45 of 49 (92%) with HBoV1 DNA in serum had a serologic diagnosis as defined by positive IgM, IgG seroconversion or an >4-fold increase in IgG, whereas 2 of 15 children (13%) with HBoV1 DNA only in their nasopharyngeal samples had serologically confirmed diagnoses.[16]

Studies using quantitative PCR and serology associate bocavirus with wheezing illnesses and pneumonia. Only a few studies have used serum bocavirus PCR in a study setting with comparison groups without respiratory tract infection. In one such study, detection of HBoV1 DNA in serum was associated with lower respiratory tract illnesses and pneumonia.[17] A serological follow-up study of 109 children from infancy to early adolescence compared the clinical events during the sampling intervals when seroconversion occurred with the next and prior intervals, and found an association between primary HBoV1 infection and respiratory tract illnesses including acute otitis media.[18] Type 2 bocavirus has been detected in stool in 3%–25% of children with gastroenteritis, but often with another enteric virus.[2,18,19] HBoV2 has been found also in stool of healthy individuals, and any association with gastroenteritis is weak. Taken together, there is substantial amount of data linking HBoV1 with upper and lower respiratory tract infections, some data linking HBoV2 with gastroenteritis and very few data linking HBoV3 or HBoV4 with any clinical illness. Studies with robust diagnostic methods in controlled populations would be needed to increase knowledge of the clinical impact of bocavirus in children and adults.

DIAGNOSIS

HBoV1 infections cannot be clinically differentiated from other viral respiratory infections. Bocavirus isolation in tissue culture is not available for diagnostic use. HBoV can be readily detected by PCR targeting NS, NP or VP genes, and it is included in several commercially available multiplex respiratory virus PCR panels. Type-specific primers or nonspecific primers followed by sequencing of the PCR product can be used for the differentiation between HBoV types. Quantitative PCR may be useful for judging the clinical

significance of bocavirus DNA detection, as higher viral loads correlate with acute infections, fewer coinfections and increased disease severity.[8,16,20] Serological methods have been developed to detect bocavirus specific IgM and IgG antibodies by utilizing recombinant capsid antigens or viral-like particles.[13,16,17,20,21] Past-immunity antibodies toward HBoV2 to 4 cross-react with HBoV1. To reliably detect seroresponses to HBoV1, this should be corrected by depletion of HBoV2–4 reactive antibodies.[15]

Acute HBoV1 infection is most reliably diagnosed by detection of DNA in serum by PCR and in respiratory tract samples by quantitative PCR, simultaneously with detection of IgM or a diagnostic IgG response in paired serum samples.[16] The value of a mere positive PCR result in nasopharyngeal sample is questionable, but very high viral copy numbers (>10^4 HBoV1 genomes/mL of nasopharyngeal aspirate) may indicate current illness.[9] HBoV2–4 viruses can be detected by PCR in stool and by serology, but correlation of virus detection with illness has not been established.

TREATMENT AND PREVENTION

No specific antiviral treatment or prevention by immunization has been reported. Currently, treatment is supportive and directed by the clinical manifestations. Standard precautions should be applied to limit the transmission of HBoV1 by respiratory secretions.

CONCLUSIONS

HBoV1 is, according to currently available information, an important causative agent of respiratory tract infections in young children. However, the disease burden caused by HBoV1 is not known yet. Diagnosis of HBoV1 infections needs critical approach and desirably combination of PCR and serological methods.

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医薬品　研究報告　調査報告書

識別番号・報告回数	E-13000001	第2報	報告日 2013年05月02日	第一報入手日 2013年04月04日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	1. 加熱人血漿たん白（6343422）		研究報告の公表状況	WHO [Internet]. Geneva: WHO RISK ASSESSMENT Human infections with avian influenza A(H7N9) virus 7 June 2013. Available from http://www.who.int/influenza/human_animal_interface/influenza_h7n9/RiskAssessment_H7N9_07Jun13.pdf	公表国 中国	
販売名（企業名）	1. プラズマプロテインフラクション（634342204）（Baxter）					

研究報告の概要

2013年3月31日以降、中国および台湾の衛生当局から計132例のH7N9型トリインフルエンザ検査確定症例が報告された。これまでに、H7型インフルエンザウイルスによるヒト感染例は少数報告されていたが、H7N9型によるヒト感染は今回が初の報告であった。中国の131例は、当初南東沿岸部に限局して発生したが、次第に北部や内陸部に拡大した。台湾の1例は、中国本土からの輸入例であると考えられた。
症状は発熱や咳等の気道感染症症状に始まり、5-7日後に呼吸困難や急性呼吸窮迫症候群を伴う重度の肺炎に至る。このウイルスは抗ウイルス薬アマンタジン、リマンタジンには抵抗性を示したが、早期のノイラミニダーゼ阻害薬による治療が有効であった。
H5N1型トリインフルエンザウイルス流行の際は、重症化した鳥類がヒト感染の警告因子となったが、H7N9型トリインフルエンザウイルスは鳥類においては軽微な症状しか示さないか無徴候であり、ヒトにおいて重症化したため、このような予測も不可能であった。H7N9型トリインフルエンザウイルス感染について、自然界で宿主となる動物種や感染経路、ヒトや動物における感染の範囲については、不明な点も多い。しかしながら、生きた家禽の取引市場およびそこから得られた家禽検体中のウイルスとヒト感染例の検体から得られたウイルスとの間に遺伝的相同性が認められたこと、大半のヒト感染例で家禽（多くはニワトリ）への曝露が報告されたこと、生きた家禽の取引市場の閉鎖および一般市民への啓蒙活動を含む公衆衛生対策実施以降に感染例が減少したことより、感染家禽およびそれらに汚染された環境が感染源であると推察された。
これまでに患者との接触者20000人以上についての調査が実施されたが、2次感染者はごくわずかであり、家族内のクラスターが数件報告されたのみであった。また、3月および4月の2か月間で、インフルエンザ様症状を呈した患者20000人以上が検査されたが、H7N9型インフルエンザウイルス感染例は6例のみであり、軽症（であるが故に報告されていない）症例が多数存在する可能性はないものと推察された。したがって、持続するヒト-ヒト感染の可能性はごく低いと考えられた。今後、同ウイルスが変異によって高いヒト感染能を獲得する可能性もあるため、同ウイルス感染の再発生時には、充分な注意が必要である。

報告企業の意見	今後の対応
これまでに、ヒトからヒトへの同ウイルスの持続的な伝播、および血液を介したヒト間感染を裏付ける根拠はない。また、同感染症の発症は中国本土および台湾に限られている。自社の血漿由来製剤はすべて米国および欧州における供血から製造されており、中国および台湾における新型インフルエンザの発生は自社品に影響しない。 以上により、現段階で特段の安全確保措置は不要であると判断した。	今後とも注意深く同感染症の発生数や頻度の変化、発生地域の拡大等の動向について情報収集に努める。

使用上の注意記載状況・その他参考事項等

自社の血漿由来製剤はすべて米国および欧州における供血から製造されている。

プラズマプロテインフラクション：該当ロットなし

［使用上の注意記載状況］
プラズマプロテインフラクション：重要な基本的注意［患者への説明］（本剤の使用にあたっては、疾病の治療における本剤の必要性とともに、本剤の製造に際し感染症の伝播を防止するための安全対策が講じられているが、ヒト血漿を原料としていることに由来する感染症伝播のリスクを完全に排除することができないことを、患者に対して説明し、理解を得るよう努めること。）

［追加・変更箇所］
2013年4月19日に研究報告として完了報告済。
2013年5月2日、ウイルスの特徴や発症症例数、転帰等につき追加情報が得られたため、追加報告をおこなった。

文献番号 3

WHO RISK ASSESSMENT
Human infections with avian influenza A(H7N9) virus
7 June 2013

Summary

Cases of H7N9 so far
A total of 132 laboratory-confirmed cases of human infection with avian influenza A(H7N9) virus have been reported to WHO; 131 cases by China National Health and Family Planning Commission and one case by the Taipei Centers for Disease Control (Taipei CDC). Although cases have been reported in both men and women, and across a wide age range, most cases have occurred in middle-aged or older men. Thirty-seven people have died, and most of the other cases were considered severe. Cases in China have been reported from Anhui, Fujian, Henan, Hunan, Jiangsu, Jiangxi, Shandong and Zhejiang, and the municipalities of Beijing and Shanghai. In addition, the case reported by Taipei CDC had a history of recent travel from Jiangsu, China.

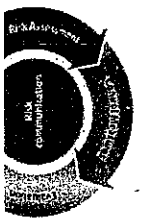
Comparison with other avian influenza viruses
This is the first time that human infection with the avian influenza A(H7N9) subtype has been detected. The few A(H7) human infections that have occurred have generally resulted in mild illness and conjunctivitis, with the exception of one death.

In outbreaks of H5N1, severely infected poultry were a warning signal for human infection. Previous sporadic cases of human infection with other influenza A(H7) viruses have also been associated with outbreaks of infection in poultry. However, since this H7N9 virus has not been reported to cause severe disease in poultry, and therefore the birds do not visibly seem to be infected, H7N9 infected birds will not likely provide a useful warning signal, and it may be difficult to determine when a person has been in contact with H7N9-infected poultry.

Source of human infection
Human infection appears to be related to exposure to live poultry or contaminated environments. However, much remains unknown about this virus, including the animal reservoir(s) in which it is circulating, the main exposures and routes of transmission, and the scope of the spread of this virus among people and animals. Investigations are ongoing.

So far, however, human infection appears to be related to exposure to live poultry or contaminated environments for the following reasons.

- The virus in humans is genetically similar to that found in birds and the environment, mostly from animal markets which sell poultry.



- Most human cases (approximately three out of four patients) report a history of exposure to birds, mostly chickens.
- The virus has been detected in poultry in live animal markets, which sell poultry.
- The number of new case reports of the disease has decreased after the implementation of public health measures, which included closure of live poultry markets and increasing public awareness.

The existence of other virus reservoirs, such as domestic or wild bird and mammalian species, has not yet been determined.

Evidence regarding human-to-human transmission
Although four small human clusters have been reported, evidence does not support sustained human-to-human transmission.

- Monitoring and testing of contacts (>2000 people) of confirmed cases has detected few infections.
- Testing of more than 20,000 people with influenza-like illness (ILI) in March and April has confirmed only six infections with H7N9. An additional case of influenza-like illness was seen in May. This suggests that milder cases of H7N9 infection are not occurring in large numbers.

Virus characteristics
Genetic and laboratory analysis of H7N9 viruses isolated from humans indicates that:

- The virus contains genes of multiple avian origin.
- Genetic analysis indicates that this H7N9 virus may have greater ability to infect mammals, including humans, than other avian influenza viruses. In addition, in laboratory testing, ferrets became infected, shed the virus, and transmitted it by direct contact.
- Sequence variations among the genes of the isolates suggest that the H7N9 virus has been introduced from animals into humans more than once.
- These viruses are in general expected to be sensitive to the neuraminidase inhibitors oseltamivir and zanamivir, but resistant to the antiviral drugs amantadine and rimantadine. Testing of one H7N9 strain (A/Shanghai/1/2013) in the neuraminidase inhibition assay yielded discrepant results. A small study has shown that the virus can develop resistance during treatment.
- The isolates have a haemagglutinin structure that is associated with low pathogenicity in birds. This has been confirmed in laboratory studies.

Risk assessment

This 7 June 2013 risk assessment has been prepared in accordance with WHO's published recommendations for rapid risk assessment of acute public health events and will be updated as more information becomes available. The risk has not changed since the previous assessment published on 10 May.

What is the risk that more human cases will occur in the affected areas?
The understanding of the epidemiology of the virus and this outbreak , including the main reservoirs of infection and the extent of geographic spread among animals, remains limited. However, it is likely that most human H7N9 infections have been associated with contacts with live animal markets that sell poultry. Further sporadic human cases should be expected in affected and possibly neighboring areas.

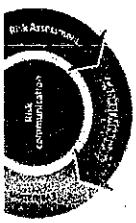
Other avian influenza viruses such as H5N1 have demonstrated a seasonal pattern in which animal outbreaks and human cases have been less frequent in summer months and more frequent in winter months in temperate zones. The number of newly reported cases has decreased over the past few weeks, but it remains to be seen whether H7N9 infections will follow the same seasonal pattern. Most human cases have resulted in clinically severe illness.

What is the risk of human-to-human transmission?
Evidence does not support sustained human-to-human transmission. However, four small clusters suggest that limited human-to-human transmission may occur where there is close contact between cases and non-infected people, as occurs in families and in healthcare settings. Moreover, the genetic changes seen among these viruses suggest that adaptation to mammals is of concern, and further adaptation may occur. Should sustained human-to-human transmission occur with an increased number of clinically severe cases, health systems are likely to be strained. WHO is providing coordination and guidance regarding provisional vaccine candidates; there are currently no recommendations on the large-scale manufacture of H7N9 vaccine.

What is the risk of international spread of H7N9 by travelers?
There is no indication that international spread has occurred, although when infected people from affected areas travel, their infection may be detected in another country. However, as the virus does not appear to cause sustained human-to-human transmission, extensive community spread is unlikely. If transmissibility were to increase, then the possibility of spread would likewise increase.

Does WHO recommend any travel and trade precautions related to H7N9?
WHO does not advise special screening at points of entry with regard to this event, nor does it currently recommend any travel or trade restrictions.

What should countries do?
WHO advises countries to continue surveillance, reporting as applicable under the IHR (2005) and other preparedness actions. Current technical information as well as guidance related to avian influenza



A(H7N9) can be found at the WHO website, http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en/.

Resources

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Additional Information

Most recent disease outbreak news can be found at: http://www.who.int/csr/don/en/index.html
Frequently Asked Questions and other information on human infections with avian influenza A(H7N9) are available at: http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en/index.html

Public health relevant virological features of influenza A(H7N9) causing human infection in China: http://www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/influenza/publications/2013/public-health-relevant-virological-features-of-influenza-ah7n9-causing-human-infection-in-china

別紙様式第2-1

No. 27

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2013. 4. 3	該当なし	

一般的名称	解凍人赤血球濃厚液	研究報告の公表状況		公表国
販売名（企業名）	解凍赤血球濃厚液「日赤」（日本赤十字社） 照射解凍赤血球濃厚液「日赤」（日本赤十字社） 解凍赤血球-LR「日赤」（日本赤十字社） 照射解凍赤血球-LR「日赤」（日本赤十字社） 解凍赤血球液-LR「日赤」（日本赤十字社） 照射解凍赤血球液-LR「日赤」（日本赤十字社）		WHO/Global Alert and Response (GAR); 1 April 2013	WHO

研究報告の概要

○中国におけるH7N9鳥インフルエンザのヒトへの感染
2013年3月31日、中国国家衛生・計画出産委員会は、WHOにインフルエンザA(H7N9)のヒト感染症例を3例報告した。これらの患者は中国疾病予防管理センターによる検査で3月29日に確定された。インフルエンザA(H3N2)、A(H1N1)pdm09、A(H5N1)及び新型コロナウイルスは全て陰性であった。患者は上海（2人）と安徽省（1人）から報告され、2013年2月19日～3月15日の間に呼吸困難を伴う重症の肺炎を発症した。2人は死亡し、1人は現在重篤な状態である。これまで患者の間に疫学的関連は確認されていない。感染源及び感染経路の調査が進められている。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-LR「日赤」
解凍赤血球液-LR「日赤」
照射解凍赤血球液-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
中国でA(H7N9)型鳥インフルエンザに3人が感染したことが確認され、そのうち2人は死亡したとの報告である。	日本赤十字社では、問診で発熱などの体調不良者を献血不適としている。また、平成21年5月18日付薬食血発第0518001号「新型インフルエンザの国内発生に係る血液製剤の安全性確保について」に基づき、新型インフルエンザの患者又は罹患の疑いのある患者と7日以内に濃厚な接触があった人の献血を制限するほか、献血後に新型インフルエンザと診断された場合には当該製剤の回収と医療機関への情報提供を行うこととしていたが、平成21年度第4回血液事業部会運営委員会において、献血血液を通じて新型インフルエンザに感染する可能性が極めて低いことが示されたことから、平成22年3月5日に廃止された。今後も引き続き情報の収集に努める。

文献番号　4

World Health Organization

Global Alert and Response (GAR)

Human infection with influenza A(H7N9) virus in China

Share Print

1 APRIL 2013 - On 31 March 2013, the China Health and Family Planning Commission notified the World Health Organization (WHO) of three cases of human infection with influenza A(H7N9). The cases were laboratory confirmed on 29 March by China CDC. Laboratory testing for influenza A (H3N2), A (H1N1)pdm09 and A(H5N1), as well as for novel coronavirus, has been negative.

The cases were reported from Shanghai (2 cases) and Anhui province (1 case). All three cases presented with respiratory tract infection with progression to severe pneumonia and breathing difficulties. Disease onset was between 19 February and 15 March 2013. Two of the cases died. The third case is currently in critical condition.

To date no epidemiological link between the cases has been identified. An investigation including follow-up of contacts is ongoing. So far no further cases have been identified among the 88 identified contacts under follow up.

Investigations into the source of infection and mode of transmission are ongoing.

The Chinese government is actively investigating this event and has instituted enhanced surveillance, laboratory strengthening and training of health care professionals for detection, reporting and treatment.

WHO is in contact with the national authorities and is following the event closely. It will issue updates as new information becomes available.

Related links

More on human infection with influenza A(H7N9) virus

番号：1

別紙様式第２－１

医薬品　研究報告　調査報告書

<table>
<tr><td>識別番号・報告回数</td><td colspan="2"></td><td>報告日</td><td>第一報入手日
2013 年 2 月 18 日</td><td>新医薬品等の区分
該当なし</td><td rowspan="3">機構処理欄</td></tr>
<tr><td>一般的名称</td><td>ﾃｸﾈﾁｳﾑ人血清ｱﾙﾌﾞﾐﾝ
(99mTc)</td><td rowspan="2">研究報告の公表状況</td><td rowspan="2">ProMED-mail
Published Date:
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20130215.1544940</td><td>公表国

イギリス</td></tr>
<tr><td>販売名（企業名）</td><td>テクネアルブミンキット
（富士フイルムＲＩファーマ株式会社）</td></tr>
<tr><td>研究報告の概要</td><td colspan="4">要約：
2013 年 2 月 11 日、英国は新型コロナウイルス感染確定例 1 例を WHO に報告した。初発症例はパキスタンおよびサウジアラビアへの最近の渡航歴のある英国住民であった。その後、同家族から追加の 2 症例が報告されたが、いずれの症例も最近の渡航歴はなかった。
同家族の 2 例目は短期間の呼吸器症状が認められ、2013 年 2 月 9 日に入院し集中治療を受けた。この症例には既存の内科的疾患があったことがわかっており、呼吸器感染症にかかるリスクが増大していた可能性がある。3 例目は 2013 年 2 月 15 日現在、軽度の呼吸器疾患から回復している。
これらの症例は、初発症例とのヒトーヒト接触を介して感染した可能性を示唆している。ただし、ほとんどの状況において、接触感染のリスクは未だ非常に低いと考えられる。
なお、この同一家族症例のうち、初発症例および２例目は死亡した。</td><td rowspan="3">使用上の注意記載状況・その他参考事項等

特になし</td></tr>
<tr><td colspan="3">報告企業の意見</td><td colspan="2">今後の対応</td></tr>
<tr><td colspan="3">新型コロナウイルスは、2012 年 9 月頃より症例が報告されていたが、感染経路については明確ではなく、ヒトーヒト感染も確認されていなかった。本報告では、英国で報告された新型コロナウイルス感染確定症例の同一家族クラスターにおいて、最近の渡航歴の無い 2 例に感染が認められ、1 例目との緊密な接触によって感染した可能性が示唆された。また同一家族症例 3 例のうち 2 例が死亡しており、死亡率も高いことから重大な感染症の可能性が高いと考えられる。本報告は、新規感染症および新規感染経路かつ重大な感染症に該当すると考えられ、感染症定期報告の対象と判断する。</td><td colspan="2">本研究報告は、ヒト血液を原料とする血漿分画製剤とは直接関連がないことから、現時点で当該生物由来製品に関し、措置等を行う必要はないと判断する。</td></tr>
</table>

MedDRA/J Version(16.0)

文献番号　5

Published Date: 2013-02-13 18:16:29
Subject: PRO/AH/EDR> Novel coronavirus - Eastern Med. (04): UK, pers to pers trans susp
Archive Number: 20130213.1541531

NOVEL CORONAVIRUS - EASTERN MEDITERRANEAN (04): UK, PERSON TO PERSON TRANSMISSION SUSPECTED
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A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

In this report:
[1] HPA press release
[2] ECDC
[3] WHO GAR update

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[1] HPA press release
Date: 13 Feb 2013
Source: HPA UK Press Release [edited]
http://www.hpa.org.uk/NewsCentre/NationalPressReleases/2013PressReleases/130213statementonlatestcoronaviruspatie

The Health Protection Agency (HPA) can confirm a further case of novel coronavirus infection in a family member of the case announced on Monday [11 Feb 2013]. The patient, who is a UK resident, does not have any recent travel history and is currently receiving intensive care treatment at The Queen Elizabeth Hospital, Birmingham. It is understood that this patient has an existing medical condition that may make them more susceptible to respiratory infections. This latest case brings the total number of confirmed cases globally to 11, of which 3 have been diagnosed in the UK.

Professor John Watson, head of the respiratory diseases department at the HPA, said: "Confirmed novel coronavirus infection in a person without travel history to the Middle East suggests that person-to-person transmission has occurred and that it occurred in the UK. This case is a family member who was in close personal contact with the earlier case and who may have been at greater risk of acquiring an infection because of their underlying health condition. To date, evidence of person-to-person transmission has been limited. Although this case provides strong evidence for person to person transmission, the risk of infection in most circumstances is still considered to be very low. If novel coronavirus were more infectious, we would have expected to have seen a larger number of cases than we have seen since the 1st case was reported 3 months ago. However, this new development does justify the measures that were immediately put into place to prevent any further spread of infection and to identify and follow up contacts of known cases. We will continue to provide advice and support to healthcare workers looking after the patients and to contacts of both cases. In light of this latest case, we would like to emphasise that the risk associated with novel coronavirus to the general UK population remains very low. The HPA will continue to work closely with national and international health authorities and will share any further advice with health professionals and the public if and when more information becomes available."

Notes to editors:

Laboratory confirmed cases to date: 11
Saudi Arabia: 5 (3 deaths)
Jordan: 2 (2 deaths)
UK: 3 (1 patient from Qatar - receiving treatment, 2 patients from UK, 1 with recent travel to Pakistan and Saudi Arabia - both receiving treatment)
Germany: 1 (patient from Qatar - discharged)

Coronaviruses are causes of the common cold but can also include more severe illness, such as SARS (severe acute respiratory syndrome). This new coronavirus was 1st identified in September 2012 in a patient who died from a severe respiratory infection in June 2012. The virus has so far only been identified in a small number of cases of acute, serious respiratory illness who presented with fever, cough, shortness of breath, and breathing difficulties.

For further information, see the HPA's coronavirus web pages, which include a Q&A page on this topic [see http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1317136202637].

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Communicated by:

ProMED-mail
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[2] ECDC Update
Date: 13 Feb 2013
Source: ECDC (European Centre for Disease Control) [edited]
http://ecdc.europa.eu/en/press/news/Lists/News/ECDC_DispForm.aspx?List=32e43ee8-e230-4424-a783-85742124029a&ID=844&RootFolder=%2Fen%2Fpress%2Fnews%2FLists%2FNews

Epidemiological update: Case of severe lower respiratory tract disease associated with a novel coronavirus:

On [13 Feb 2013], the HPA announced that one family contact of the previously-confirmed case reported on [11 Feb 2013] was laboratory-confirmed to be infected with the novel coronavirus (NCoV). This 2nd case from the same family was hospitalised on [9 Feb 2013] with a short history of respiratory symptoms. The patient has an existing medical condition that may make him more susceptible to respiratory infections. He does not have a recent travel history and is currently receiving intensive care treatment.

The cases have been notified through the EU alerting system for communicable diseases.

This brings the total of laboratory-confirmed cases of severe pneumonia caused by the NCoV to 11 globally (see table below).

The information available suggests human-to-human transmission of the NCoV in this family cluster.

The HPA reports that surveillance of family, close contacts of the 2 patients, and healthcare workers treating the 2 patients is ongoing, as per the UK National Guidelines. None are currently presenting with symptoms consistent with NCoV.

The HPA is also following-up regarding passengers who may have been exposed while flying with the case announced on [11 Feb 2013] and are in contact with the airline concerned.

In light of this human-to-human transmission of the NCoV within the family cluster, ECDC is now updating its risk assessment, previously published on [7 Dec 2012].

Case No: Date Onset / Age (years) / Sex / Probable place of infection / Date reported / Source / Outcome

1: April 2012 / 45/ F / Jordan** / 30 Nov 2012 / WHO/IHR / Dead

2: April 2012 / 25 / M / Jordan** / 30 Nov 2012 / WHO/IHR / Dead

3: 13 Jun 2012 / 60 / M / Kingdom of Saudi Arabia* / 20 Sep 2012 / Kingdom of Saudi Arabia, ProMED / Dead

4: 3 Sep 2012 / 49 / M / Qatar / Kingdom of Saudi Arabia*** / 22 Sep 2012 / HPA/WHO / Alive

5: NK / NK / NK / Kingdom of Saudi Arabia* / 4 Nov 2012 / Kingdom of Saudi Arabia, ProMED, SMJ / Alive

6: 12 Oct 2012 / 45 / M / Qatar**** / 23 Nov 2012 / RKI/WHO / Alive

7: NK / NK / M / Kingdom of Saudi Arabia* / 19-23 Nov 2012 / Kingdom of Saudi Arabia, ProMED, WHO / Alive

8: 28 Oct 2012 / NK / M / Kingdom of Saudi Arabia* / 23 Nov 2012 / WHO / Dead

9: October 2012 / NK / M / Kingdom of Saudi Arabia* / 28 Nov 2012 / WHO / Dead

10: 24 Jan 2013 / 60 / M / Pakistan, Kingdom of Saudi Arabia*/ 8 Jan 2013 / EWRS / Alive, Hospitalised

11: 6 Feb 2013 / NK / M / United Kingdom* / 12 Feb 2013 / HPA / Alive, Hospitalised

* Part of family cluster
** Healthcare worker and part of outbreak linked to hospital
*** Patient transferred to UK
**** Patient transferred to Germany
NK: not known

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Communicated by:
ProMED-mail
<promed@promedmail.org>

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[3] WHO GAR update

Date: 13 Feb 2013
Source: WHO GAR [edited]
http://www.who.int/csr/don/2013_02_13/en/index.html

Novel coronavirus infection - update [13 Feb 2013]:

The United Kingdom (UK) has informed WHO of another confirmed case of infection with the novel coronavirus (NCoV). The patient is a UK resident and a relative of the case announced on [11 Feb 2013].

The latest confirmed case does not have any recent travel history outside the UK and is currently hospitalized in an intensive care unit. It is understood that this patient has pre-existing medical conditions that may have increased susceptibility to respiratory infections.

Confirmed NCoV in a person without recent travel history indicates that infection was acquired in the UK. To date, evidence of person-to-person transmission has been limited. Although this case is suggestive of person-to-person transmission, on the basis of current evidence, the risk of sustained person-to-person transmission appears to be very low.

The Health Protection Agency (HPA) is following up on all close contacts (family and healthcare workers) who may have been exposed to either of these 2 new confirmed cases.

As of [13 Feb 2013], a total of 11 confirmed cases of human infection with NCoV have been notified to WHO, with no change in the number of fatalities i.e., 5 deaths since April 2012.

Based on the current situation and available information, WHO encourages all Member States to continue their surveillance for severe acute respiratory infections (SARI) and to carefully review any unusual patterns. Testing for the new coronavirus should be considered in patients with unexplained pneumonias, or in patients with unexplained severe, progressive, or complicated respiratory illness not responding to treatment.

Any clusters of SARI or SARI in healthcare workers should be thoroughly investigated, regardless of where in the world they occur.

New cases and clusters of the NCoV should be reported promptly both to national health authorities and to WHO.

WHO does not advise special screening at points of entry with regard to this event nor does it recommend that any travel or trade restrictions be applied.

WHO continues to monitor the situation closely.

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Communicated by:
ProMED-mail Rapporteur Marianne Hopp

[The above mentioned case of severe acute respiratory infection (SARI) is currently the 11th confirmed case of severe respiratory disease attributable to infection with the novel CoV 1st identified in a fatal case in Saudi Arabia (see prior ProMED-mail posts listed below). It is also the 3rd incident of infection with this novel CoV that occurred in a close contact of an earlier confirmed case, suggesting possible person to person transmission of the virus. There was a cluster of 3 confirmed cases in a family in Saudi Arabia in November 2012 and a cluster of 2 confirmed cases among ICU staff in a hospital in Jordan in May 2012. As stated clearly in the 3 reports of this update, evidence thus far does not seem to suggest an ease and facility of person-to-person contact of this organism as yet.

The table of cases presented in the ECDC report above is a very useful presentation and summary of the current publicly available information on the descriptive epidemiology of known confirmed cases of severe acute respiratory illness due to infection with this novel CoV. Information on exposure histories of each of the patients is not available (some of the earlier cases were reported to have had contact with farm animals in Saudi Arabia and Qatar, but similar information was not available on all cases). To date, cases that have been confirmed have been linked to geographic presence in the Middle East prior to onset of illness (Jordan, Saudi Arabia or Qatar; with one case also having visited Pakistan during the period prior to onset of illness). The absence of cases reported from other areas among individuals without history of contact with this region of the world may or may not reflect the true geographic distribution of this novel CoV, as there may be a bias against testing for this virus in the absence of such stated exposure history ("seek and ye shall find," or the corollary, "don't look and you won't find").

The scientific community is eagerly awaiting the details of epidemiologic investigations conducted on the 11 previously confirmed cases of infection with the novel CoV, especially those addressing exposure to possible animal sources (bats, bat saliva and excrement, farm animals, etc.) and dates of contacts/dates of onset of previous clusters. In addition, information on field studies on bats and farm animals in the Middle Eastern countries addressing infection of animals with the novel CoV is eagerly awaited as well.

For the interactive HealthMap/ProMED map of the UK, see http://healthmap.org/r/1INY. For the interactive HealthMap/ProMED map of the Middle East, see http://healthmap.org/r/1HAJ. - Mod.MPP]

See Also

Novel coronavirus - Eastern Med. (03): Saudi comment 20130212.1540011
Novel coronavirus - Eastern Med. (02): UK ex Saudi Arabia, Pakistan 20130212.1539086
Novel coronavirus - Eastern Mediterranean: bat reservoir 20130122.1508656
2012

Novel coronavirus - Eastern Mediterranean (06): comments 20121225.1468821
Novel coronavirus - Eastern Mediterranean (05): WHO, transmission route 20121223.1465597
Novel coronavirus - Eastern Mediterranean (04): receptor charact. 20121211.1446670
Novel coronavirus - Eastern Mediterranean (03): research, ISARIC (UK) 20121208.1443486
Novel coronavirus - Eastern Mediterranean (02): diagnostics 20121207.1442473
Novel coronavirus - Eastern Mediterranean: WHO, Jordan, conf., RFI 20121130.1432498
Novel coronavirus - Saudi Arabia (19): Singapore: NOT 20121129.1430397
Novel coronavirus - Saudi Arabia (18): WHO, new cases, cluster 20121123.1421664
Novel coronavirus - Saudi Arabia (17): 4th case, RFI 20121121.1418018
Novel coronavirus - Saudi Arabia (16): whole genome sequence 20121114.1409556
Novel coronavirus - Saudi Arabia (15): new case 20121104.1391285
Novel coronavirus - Saudi Arabia (14): KSA MOH 20121022.1358297
Novel coronavirus - Saudi Arabia (13): history, collateral damage 20121021.1356623
Novel coronavirus - Saudi Arabia (12): RFI 20121019.1353615
Novel coronavirus - Saudi Arabia (11): clin. lab. & epi. investigations 20121004.1324712
Novel coronavirus - Saudi Arabia (10): WHO, revised case def. 20120930.1315960
Novel coronavirus - Saudi Arabia (09): real-time RT-PCR, addition 20120929.1315725
Novel coronavirus - Saudi Arabia (08): real-time RT-PCR assay 20120928.1314254
Novel coronavirus - Saudi Arabia (07): Eurosurveillance reports 20120928.1313337
Novel coronavirus - Saudi Arabia (06) 20120927.1311743
Novel coronavirus - Saudi Arabia (05): WHO, case def., nomenclature 20120926.1309747
Novel coronavirus - Saudi Arabia (04): RFI, Jordan, April 2012 20120925.1308001
Novel coronavirus - Saudi Arabia (03): UK HPA, WHO, Qatar 20120923.1305982
Novel coronavirus - Saudi Arabia (02): additional cases, RFI 20120923.1305931
Novel coronavirus - Saudi Arabia: human isolate 20120920.1302733
.....mpp/msp/dk

Published Date: 2013-02-15 21:42:23
Subject: PRO/AH/EDR> Novel coronavirus - Eastern Mediterranean (05): UK,3rd case,
Archive Number: 20130215.1544940

NOVEL CORONAVIRUS- EASTERN MEDITERRANEAN (05): UK, 3RD CASE
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A ProMED-mail post
http://www.promedmail.org
ProMED-mail is a program of the
International Society for Infectious Diseases
http://www.isid.org

Date: 15 Feb 2013
Source: HPA Press Release [edited]
http://www.hpa.org.uk/NewsCentre/NationalPressReleases/2013PressReleases/1302153rdcaseofcoronavirus/

Third case of novel coronavirus infection identified in family cluster
[15 Feb 2013]

The Health Protection Agency (HPA) can confirm a 3rd case of novel coronavirus infection in a family cluster, following the confirmed diagnosis of 2 cases announced earlier this week. The patient, who is a UK resident and does not have any recent travel history, is recovering from a mild respiratory illness and is currently well. This latest case brings the total number of confirmed cases globally to 12, of which 4 have been diagnosed in the UK.

Professor John Watson, head of the respiratory diseases department at the HPA, said: "Although this patient had a mild form of respiratory illness, as a precaution the HPA is advising that the patient self-isolate and limit contact with non-household members. Follow up of other household members and contacts of this case is currently underway.

"Although this case appears to be due to person-to-person transmission, the risk of infection in contacts in most circumstances is still considered to be low. If novel coronavirus were more infectious, we would have expected to have seen a larger number of cases than we have seen since the 1st case was reported 3 months ago. However, this new development does justify the measures that were immediately put into place to prevent any further spread of infection and to identify and follow up contacts of known cases.

"We would like to emphasise that the risk associated with novel coronavirus to the general UK population remains very low. The HPA will continue to work closely with national and international health authorities and will share any further advice with health professionals and the public if and when more information becomes available."

ENDS

Notes to editors:

1. Laboratory confirmed cases to date: 12

Saudi Arabia: 5 (3 deaths)
Jordan: 2 (2 deaths)
UK: 4 (1 patient from Qatar - receiving treatment, 3 patients from UK, 2 receiving treatment, 1 recovered)
Germany: 1 (patient from Qatar - discharged)
2. Coronaviruses are causes of the common cold but can also include more severe illness, such as SARS (Severe Acute Respiratory Syndrome). This new coronavirus was first identified in September 2012 in a patient who died from a severe respiratory infection in June 2012. The virus has so far only been identified in a small number of cases of acute, serious respiratory illness who presented with fever, cough, shortness of breath, and breathing difficulties.

3. For further information, see the HPA's coronavirus webpages [http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/NovelCoronavirus2012/] which includes a Q&A [http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/NovelCoronavirus2012/GeneralInformation/respqandano on this topic.

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Communicated by:
ProMED-mail
<promed@promedmail.org>

[This case represents the 12th confirmed case of respiratory illness associated with infection with the novel coronavirus (nCoV) and the 3rd case in a family cluster in the UK (see prior ProMED-mail posts listed below). There have been 2 prior clusters of respiratory illness associated with the nCoV - one cluster with 2 fatalities confirmed involving ICU (Intensive care unit) staff in a hospital in Jordan in May 2012 and the 2nd family cluster in Saudi Arabia in November 2012. In the latter case, information was not available to determine if the cluster was due to common exposures or person-to-person transmission. In this cluster in the UK, the dates of onset of the cases are sequential and only the 1st case had the known risk factor of travel to Saudi Arabia where earlier cases have been identified. Hence it is fairly certain that there has been thus far limited person-to-person transmission.

For the interactive map ofFor the interactive HealthMap/ProMED map of the UK, see http://healthmap.org/r/1INY. For the interactive HealthMap/ProMED map of the Middle East, see http://healthmap.org/r/1HAJ. - Mod.MPP]

A HealthMap/ProMED-mail map can be accessed at: http://healthmap.org/r/1INY.]

See Also

Novel coronavirus - Eastern Med. (04): UK, pers to pers trans susp 20130213.1541531
Novel coronavirus - Eastern Med. (03): Saudi comment 20130212.1540011
Novel coronavirus - Eastern Med. (02): UK ex Saudi Arabia, Pakistan 20130212.1539086
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Novel coronavirus - Eastern Mediterranean: WHO, Jordan, conf., RFI 20121130.1432498
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Novel coronavirus - Saudi Arabia (02): additional cases, RFI 20120923.1305931
Novel coronavirus - Saudi Arabia: human isolate 20120920.1302733
.....mpp/dk

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2013 年 04 月 05 日	新医薬品等の区分 該当なし		厚生労働省処理欄
一般的名称	①②ポリエチレングリコール処理抗破傷風人免疫グロブリン ③乾燥抗破傷風人免疫グロブリン			研究報告の公表状況	International Journal of Infectious Diseases 2013; 17(3): 206-208	公表国 中国	
販売名 (企業名)	①テタノブリン IH 静注 250 単位　(日本血液製剤機構) ②テタノブリン IH 静注 1500 単位　(日本血液製剤機構) ③テタノブリン筋注用 250 単位　(日本血液製剤機構)						

研究報告の概要

1. 緒　　言

2007 年から現在まで、発熱、血小板減少症、及び白血球減少症候群の何百もの症例が、湖北省を含む中国の 6 つの省で報告されている。これは重症熱性血小板減少症候群（SFTS）と名付けられた新興感染症で、SFTS ブニヤウイルス（SFTSV）と呼ぶブニヤウイルスの新型によって引き起こされる。SFTS は一般に散発症例として起こり、集団症例は頻繁に起こらない。

我々は 2012 年の 5・6 月の間に湖北省の丘陵の村で発生し SFTSV に起因したヒトーヒト感染の SFTS 症例の集団を報告する。発端患者は典型的な発熱、血小板減少、及び白血球減少を呈し、そして入院したが、残念ながら死亡した。彼の死後、3 人の二次患者は発端患者の血液及び/又は血性分泌物に触れた、或いは暴露した後の 7-12 日で相次いで病気になった。3 人の二次患者は全員臨床確認診断を受けた。

2. 症例報告－臨床的特徴と疫学

発端患者は 2012 年 5 月 6 日に悪寒、咽頭痛、吐き気、嘔吐、及び腹痛を伴う 39.3℃の発熱を突然発症した 63 歳の老人であった。通常の血液検査は、白血球減少と血小板減少を示した（白血球(WBC)数 1.25×10^9/L と血小板 87×10^9/L）。彼は 5 月 7 日に地元の病院の血液科に入院し、リバビリン、セフロキシム、及びヒト顆粒球コロニー刺激因子－刺激クローンを投与された。腹部の非造影高解像度のコンピューター断層撮影（CT スキャン）は異常所見を示さなかった。顆粒球の 65.0%と共に有核細胞と巨核球の明らかな増殖は、骨髄細胞診で見つかった。しかし、臨床的改善が観察されず、下血と全身性筋肉痛が発症した。広域スペクトル抗生物質、顆粒球コロニー刺激因子療法、そして血小板とヒト免疫グロブリンの注入を含む一連の戦略への反応がなかった。胃腸の出血が持続し、彼の血小板数と白血球数は次第に減少した。発熱の発症後の 6 日目に、白血球数は 1.19×10^9/L に、そして血小板は 40×10^9/L に減少した。患者は深い昏睡状態にあり、時折痙攣した。彼の皮膚は出血していた。気管挿管と侵襲人工呼吸が行われた。それでも、蘇生治療は効果がなかった。彼の親戚は患者が病院で死ぬことを望まなかった、そして定位置に気管内挿管と静脈注で彼の故郷に彼を戻した。家に到着後、半時間で発端患者は死亡した。これは病気の発症後、7 日目の 5 月 12 日であった。彼は発熱、血小板減少、及び白血球減少を含む典型的な臨床 SFTS 症状であったが、SFTS 診断はされなかった。

彼の死後、彼の二人の兄弟（症例 1 と症例 2）は、任意の予防措置を取ることなく、彼のメイクアップを行った。症例 1 は彼の気管チューブを取り外し、症例 2 は彼の静脈針を抜いた。両名は、このプロセスの間気道において発端患者の血液や血性分泌物に触れた。症例 3 は、発端患者の血まみれの服をきれいにするのを手伝っている間に、彼の血性分泌物に接触した。3 つの症例は曝露後 7-12 日で発症し、相次いで病気に罹った。彼らは 3 つの病院で 3 異なる部門に入院した。2 症例は死亡した（症例 1 と症例 2）。

同じ村において、そして発熱、血小板減少、及び白血球減少を含む典型的な臨床症状を持つ全ての症例を伴うこの流行での症例のクラスター分析のために、SFTS の高い疑いがあった。二次症例の全てからの血液サンプルは、湖北省の疾病管理予防センターに送られた。3 人の二次患者は、リアルタイム逆転写ポリメラーゼ連鎖反応（RT-PCR）及びウイルス分離によって検査で確定された SFTS の診断を得た。発端患者は、誤診と血清サンプルの不足のために病原体を分析されなかった。発端者と 3 人の二次患者の臨床的特徴を表 1 に示す。

3 箇月間の追跡調査の後、保護的な予防策を取った人、及び挿管を行っている 3 人の集中治療室（ICU）の医師（3 つの異なる病院で働く）と 21 人の看護師を含む、患者と接触した人は、病気になっていない。病気の発症から発端患者の葬式まで彼に暴露した別の 58 人は、彼の分泌物に直接触れておらず、病気になっていない。また、同じ村の 223 人の別の住民で新たな症例は発生していない。

使用上の注意記載状況・その他参考事項等

代表としてテタノブリン IH 静注 250 単位の記載を示す。

2. 重要な基本的注意

(1) 本剤の原材料となる血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体陰性であることを確認している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の破傷風抗毒素を含有する血漿を原料として、Cohn の低温エタノール分画で得た画分からポリエチレングリコール 4000 処理、DEAE セファデックス処理等により抗破傷風人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

文献番号 6

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

3. 議　　論

我々は、疫学データがヒトーヒト感染の特徴を示す検証済み SFTS の 3 人の患者と推定 SFTS の一人の患者のグループを公表した。ダニ咬傷は彼らの誰からも報告されていない。発端症例は典型的な SFTS の特徴を持っていたが、彼は誤診と血清サンプルの不足のために病原体を分析されていない。彼の二人の兄弟と隣人は相次いで病気になり、そして彼の血液や分泌物に接触したことで、病因診断で SFTS を持っていると確認された。彼の兄弟は死亡した。3 箇月間の追跡調査の後、患者に曝されていたが、患者の分泌物に直接触れていなかった人達では SFTS 患者は同定されなかった。SFTSV はリアルタイム RT-PCR で同定されなかった、そして SFTSV に対する抗体は、同じ部屋に滞在した 13 人の暴露した親戚や隣人、及び 42 人の医療スタッフ（3 人の ICU 医師と 21 人の看護師を含む）、或いは同じ部屋に泊まっていた患者から採取した血清サンプルで同定されなかった。また、同じ村の 223 人の別の住民で新たな症例は発生していない。

この新しく認識された疾患の臨床診断及び鑑別診断は非常に重要である。SFTS は、ヒトアナプラズマ症、腎症候性出血熱、及びレプトスピラ症など他の感染症から臨床的に区別する必要がある。SFTS の症状は非特異的であった。鍵となる臨床的特徴は、発熱、血小板減少症、胃腸症状、白血球減少症、及び多臓器不全症候群（MODS）が含まれる。臨床検査に関する最も一般的な異常は血小板減少症と白血球減少症であった。白血球数と血小板数は次第に低下することがある。MODS は急に重症症例に発展することがあり、死亡の原因となる。このグループでは、4 人の患者全員が誤診され、血液学、心臓病学、消化器外科、及び呼吸器を含む 4 つの異なる部門に入院した。

SFTS の感染経路は不明である。重要な問題は、SFTSV が、ヒトからヒトへ感染することができるかどうかである。ウイルスのヒトーヒト感染の幾つかの疫学及び分子的証拠がある。これは、急性期の血清サンプル及び死体血と血性分泌物が接触感染性であると推測された。血液や血性排泄物と直接接触する人は SFTSV に感染することができる。我々のデータに基づき、3 人の二次症例全員は保護されていない皮膚や粘膜を通して血液と接触する可能があった、これが理由で我々は SFTSV が患者の死体血液や血性分泌物との接触を介してヒトからヒトへ感染することができると結論付けた。これはまた SFTSV 感染血液が患者の死後でさえ、長期間感染性が続く可能性を示している。

より多くの重視がこの疾患に与えられるべきで、医療従事者の更なる訓練が、特に流行地域において、誤診を防ぐために行われるべきである。

報告企業の意見	今後の対応
重症熱性血小板減少症候群ウイルス（severe fever with thrombocytopenia syndrome virus：SFTSV）はブニヤウイルス科（bunyaviridae）フレボウイルス属（phlebovirus）に分類される 2009 年に中国で発見されたウイルスである。フレボウイルスのビリオンは直径 92～105nm の球形で、脂質エンベロープを有する RNA ウイルスである。万一、原料血漿に SFTSV が混入したとしても、HIV-1（Human immunodeficiency virus-1）をモデルウイルスとしたウイルスクリアランス試験結果から、本剤の製造工程において不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

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Case Report

A cluster of cases of human-to-human transmission caused by severe fever with thrombocytopenia syndrome bunyavirus

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SUMMARY

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease in six epidemic provinces of China and was identified to be caused by a novel bunyavirus in 2009. It is progressive in nature and potentially fatal. SFTS usually occurs as sporadic cases and is considered a tick-transmitted disease. Here we present a group of three patients with proven SFTS and one with probable SFTS, for whom the epidemiological data show person-to-person transmission characteristics. The index patient and two secondary patients died. None reported a tick bite.

1. Introduction

From 2007 to date, hundreds of cases of a fever, thrombocytopenia, and leukopenia syndrome have been reported in six provinces of China, including Hubei.[1] This is an emerging infectious disease that has been named severe fever with thrombocytopenia syndrome (SFTS) and is caused by a new type of bunyavirus, called SFTS bunyavirus (SFTSV).[1,2] SFTS usually occurs as sporadic cases, and clustered cases occur less frequently.

We report a cluster of SFTS cases of human-to-human transmission caused by the SFTSV that occurred in a hilly village of Hubei Province between May and June in 2012. The index patient presented the typical fever, thrombocytopenia, and leukopenia and was hospitalized, but unfortunately he died. After his death, three secondary patients successively became ill at 7–12 days after contact or exposure to the index patient's blood and/or bloody secretions. All three secondary patients had laboratory-confirmed diagnoses.

2. Case reports—clinical features and epidemiology

The index patient was a 63-year-old man who had a sudden onset of fever on May 6, 2012, with a temperature of 39.3 °C, accompanied by chills, pharyngeal pain, nausea, vomiting, and abdominal pain. Routine blood tests showed leukopenia and thrombocytopenia (white blood cell (WBC) count 1.25×10^9/l and platelets 87×10^9/l). He was admitted to the Department of Hematology of the local hospital on May 7, and was administered ribavirin, cefuroxime, and human granulocyte colony-stimulating factor-stimulated clone. A non-contrast high-resolution computed tomography scan of the abdomen showed no abnormal findings. Obvious proliferation of nucleated cells and megakaryocytes with 65.0% of granulocytes was found on bone marrow cytology. However, no clinical improvement was observed and melena and generalized myalgia developed. There was no response to a series of strategies, including broad-spectrum antibiotics, granulocyte colony-stimulating factor therapy, and blood platelet and human immunoglobulin infusion. The gastrointestinal bleeding persisted and his platelet count and WBC count declined progressively. On day 6 after the onset of fever, the WBC count had decreased to 1.19×10^9/l and platelets to 40×10^9/l. The patient was in a deep coma and occasionally had convulsions. His skin was bleeding. Tracheal intubation and invasive mechanical ventilation was performed. Even so, resuscitation therapies were not effective. His relatives did not want the patient to die in hospital and returned him to his hometown with the endotracheal intubation and intravenous infusions in place. Half an hour after arriving home, the index patient died. This was on May 12, at day 7 after the onset of the disease. Although he had typical clinical SFTS symptoms including fever, thrombocytopenia, and leukopenia, the SFTS diagnosis was not made.

After his death, his two brothers (case 1 and case 2) did his make-up without taking any protective precautions. Case 1 removed his tracheal tube and case 2 withdrew his intravenous

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Table 1
Clinical features of a cluster of severe fever with thrombocytopenia syndrome patients

	Index patient	Case 1	Case 2	Case 3
General data				
Sex	Male	Male	Male	Female
Age, years	63	66	61	59
Date of onset	May 6, 2012	May 23, 2012	May 19, 2012	May 24, 2012
Outcome	Death	Death	Death	Discharge
Date of death or discharge	May 12, 2012	May 28, 2012	June 1, 2012	June 6, 2012
Length after onset, days	7	7	13	14
Symptoms and signs				
Maximal temperature, °C	39.6	40.2	40.6	39.8
Nausea and vomiting	Yes	No	Yes	No
Bleeding	Yes	Yes	Yes	Yes
Abdominal pain	Yes	No	Yes	No
Diarrhea	Yes	No	No	Yes
Malaise	Yes	Yes	Yes	Yes
Confusion	Yes	Yes	Yes	No
Conjunctival congestion	Yes	Yes	Yes	No
Lymphadenopathy	Yes	No	No	No
Laboratory findings				
Platelets, $\times 10^9$/l				
Onset	104	47	65	74
Min	40	28	13	48
White blood cell count, $\times 10^9$/l				
Onset	1.39	1.69	2.65	2.69
Min	1.11	1.06	1.48	2.02
Alanine aminotransferase, U/l	326	289	646	136
Aspartate aminotransferase, U/l	543	257	340	184
Total protein, g/l	65.10	70.10	68.30	74.50
Albumin, g/l	29.30	35.20	28.40	33.20
Blood urea nitrogen, mmol/l	5.33	5.99	5.30	3.90
Creatinine, μmol/l	57.42	67.90	78.22	68.40
Lactate dehydrogenase, U/l	2022	1207	1578	605
Creatine kinase, IU/l	2113	729	326	106
Creatine kinase-MB fraction, ng/ml	15.42	54.57	12.65	2.15
Ultra-sensitivity cardiac troponin I, ng/ml	2.13	>50.00	1.65	0.10
Myoglobin, μg/l	243.33	>1000.00	189.52	172.74
N-terminal pro-brain natriuretic peptide, pg/ml	403.30	1165.70	786.60	325.80
Activated partial thromboplastin time, s	101.2	125.20	63.5	87.1
D-dimer, mg/l	49.92	29.40	9.03	8.63
C-reactive protein, mg/l	14.10	25.00	23.40	13.60
Procalcitonin	0.67	0.96	1.22	0.51
Multiple organ dysfunction syndrome	Yes	Yes	Yes	No
Hematuria[a]	+++	++	++	+
Proteinuria[a]	+++	++	++++	+
Virus isolation	No data	Yes	Yes	Yes
Real-time RT PCR	No data	Positive	Positive	Positive

RT-PCR, reverse transcriptase polymerase chain reaction.
[a] Possible results are: –, negative; +, weak positive; ++, positive; +++, strong positive.

needles. Both of them came into contact with the index patient's blood or bloody secretions in the airway during this process. Case 3 came into contact with the index patient's bloody secretions while helping to clean his bloody clothes. The three cases successively fell ill, with onset 7–12 days after exposure. They were admitted to three different departments in three hospitals. Two of the cases died (case 1 and case 2).

Due to the clustering of cases in this outbreak in the same village, and with all cases having typical clinical symptoms including fever, thrombocytopenia, and leukopenia (Table 1), there was a high suspicion of SFTS. Blood samples from all of the secondary cases were sent to the Hubei Province Center for Disease Control and Prevention. The three secondary patients had laboratory-confirmed SFTS diagnoses by real-time reverse transcriptase polymerase chain reaction (RT-PCR) and virus isolation. The index patient was not analyzed for the pathogen because of misdiagnosis and the lack of a serum sample. The clinical features of the index patient and three secondary patients are listed in Table 1.

After 3 months of follow-up, no persons who took protective precautions and who had been in contact with the patients, including the three intensive care unit (ICU) doctors (working in three different hospitals) performing intubations and 21 nurses, had become ill. Fifty-eight other individuals who had been exposed to the index patient from the onset of the illness until his funeral ceremony, but who had not directly touched his secretions, had not become ill. Also, no new case occurred in the 223 other inhabitants of the same village.

3. Discussion

We have presented a group of three patients with proven SFTS and one with probable SFTS, for whom epidemiological data show person-to-person transmission characteristics. No tick bite was reported by any of them. Although the index case had typical SFTS features, he was not analyzed for the pathogen because of misdiagnosis and the lack of a serum sample. Two of his brothers and a neighbor successively became ill and were confirmed as having SFTS by etiological diagnosis, having come into contact with his blood or secretions. His brothers died. After 3 months of follow-up, no patients with SFTS were identified in those who had been exposed to the patients but who had not directly touched their secretions. No SFTSV was identified on real-time

RT-PCR and no antibodies against SFTSV were identified in serum samples collected from 13 exposed relatives and neighbors, 42 medical staff (including the three ICU doctors and 21 nurses), or patients staying in the same rooms. Also, no new case occurred in the 223 other inhabitants of the same village.

The clinical diagnosis and differential diagnosis of this newly recognized disease are of great importance. SFTS needs to be differentiated clinically from other infectious diseases, such as human anaplasmosis, hemorrhagic fever with renal syndrome, and leptospirosis.[1] The symptoms of SFTS were nonspecific. The key clinical features include fever, thrombocytopenia, gastrointestinal symptoms, leukocytopenia, and multiple organ dysfunction syndrome (MODS).[1] The most common abnormalities on laboratory testing were thrombocytopenia and leukocytopenia. WBC and platelet counts may progressively decrease. MODS can develop rapidly in severe cases and become the cause of death. In this group, all four patients were misdiagnosed and were admitted to four different departments, including hematology, cardiology, gastrointestinal surgery, and respirology.

The transmission route of SFTS remains unclear. An important question is whether SFTSV can be transmitted from person to person. There is some epidemiological and molecular evidence of person-to-person transmission of the virus.[3–5] It is speculated that the acute-phase serum samples and cadaveric blood and bloody secretions are contagious. Persons who come into direct contact with blood or bloody discharge can be infected with SFTSV. Based on our data, all three secondary cases had possible blood contact through unprotected skin and mucosa, and hence we conclude that SFTSV can be transmitted from human-to-human through contact with the patient's cadaveric blood or bloody secretions. This also indicates that SFTSV-infected blood may remain infectious for a long time, even after patient death.

More emphasis should be given to this disease and further training of medical personnel should be carried out to prevent misdiagnosis, especially in epidemic areas.

Conflict of interest: The authors have declared that there are no conflicts of interest.

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医薬品　研究報告　調査報告書

識別番号・報告回数		報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
			2013年5月27日	該当なし。	
一般的名称	別紙のとおり。	研究報告の公表状況	WHO Global Alert and Response 2013;May 17	公表国 イギリス	
販売名（企業名）	別紙のとおり。				

研究報告の概要

問題点：新規コロナウイルスにおいて限定的ながら初めて人-人感染が認められた。

新規コロナウイルスの人感染について、これまでに40例が確定されており、中東以外に欧州のフランス、ドイツ、イギリスでも症例が報告されている。欧州の症例は直接または間接に中東との関連が示されているものの、フランスとイギリス例は中東への渡航歴は無く、中東へ渡航した者との接触が見られた例である。2013年5月10日時点の確定例の多くが入院を要する重大な急性の呼吸器疾患を有しており、40例中20例が死亡例である。これまでに報告された一部集団における感染は家族内または医療現場で発生しており、少なくともこれらの集団では人-人感染が生じているが、感染形態は不明である。これまでに一部集団を超えて地域社会へ伝播したことを示す兆候は見られていない。

報告企業の意見	今後の対応
別紙のとおり。	今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

使用上の注意記載状況・その他参考事項等

記載なし。

MedDRA/J ver.16.0

文献番号 7

別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免役グロブリン、⑤人免役グロブリン、⑥乾燥ペプシン処理人免疫グロブリン、⑦乾燥スルホ化人免疫グロブリン、⑧乾燥スルホ化人免疫グロブリン、⑨乾燥スルホ化人免疫グロブリン、⑩乾燥スルホ化人免疫グロブリン、⑪乾燥スルホ化人免疫グロブリン*、⑫乾燥濃縮人活性化プロテインC、⑬乾燥濃縮人血液凝固第Ⅷ因子、⑭乾燥濃縮人血液凝固第Ⅷ因子、⑮乾燥濃縮人血液凝固第Ⅷ因子、⑯乾燥濃縮人血液凝固第Ⅸ因子、⑰乾燥濃縮人血液凝固第Ⅸ因子、⑱乾燥濃縮人血液凝固第Ⅸ因子、⑲乾燥抗破傷風人免疫グロブリン、⑳抗 HBs 人免疫グロブリン、㉑トロンビン、㉒フィブリノゲン加第ⅩⅢ因子*、㉓フィブリノゲン加第ⅩⅢ因子、㉔乾燥濃縮人アンチトロンビンⅢ、㉕ヒスタミン加人免疫グロブリン製剤、㉖人血清アルブミン*、㉗人血清アルブミン*、㉘乾燥ペプシン処理人免役グロブリン*、㉙乾燥濃縮人アンチトロンビンⅢ
販売名（企業名）	①献血アルブミン 20 “化血研”、②献血アルブミン 25 “化血研”、③人血清アルブミン “化血研” *、④ガンマーグロブリン筋注 450mg/3mL「化血研」、⑤ガンマーグロブリン筋注 1500mg/10mL「化血研」、⑥献血グロブリン注射用 2500mg「化血研」、⑦献血ベニロン－Ⅰ静注用 500mg、⑧献血ベニロン－Ⅰ静注用 1000mg、⑨献血ベニロン－Ⅰ静注用 2500mg、⑩献血ベニロン－Ⅰ静注用 5000mg、⑪ベニロン*、⑫注射用アナクトC2,500 単位、⑬コンファクトF注射用 250、⑭コンファクトF注射用 500、⑮コンファクトF注射用 1000、⑯ノバクトM静注用 400 単位、⑰ノバクトM静注用 800 単位、⑱ノバクトM静注用 1600 単位、⑲テタノセーラ筋注用 250 単位、⑳ヘパトセーラ筋注 200 単位/mL、㉑トロンビン “化血研”、㉒ボルヒール*、㉓ボルヒール組織接着用、㉔アンスロビンP500 注射用、㉕ヒスタグロビン皮下注用、㉖アルブミン 20%化血研*、㉗アルブミン 5%化血研*、㉘静注グロブリン*、㉙アンスロビンP1500 注射用
報告企業の意見	コロナウイルスは 80～160nm の球形または楕円形で、核酸は一本鎖 RNA、エンベロープを有し、感染しても軽度の風邪症状程度と考えられていたが、2003 年に発生した重症急性呼吸器症候群（SARS: severe acute respiratory syndrome）の原因ウイルスがコロナウイルス科のウイルスであったことが判明している。 今回の報告は、急性の呼吸器症候群の原因ウイルスとして同定された新規なコロナウイルスにおいて、限定的ながら初めて人-人感染が認められた、との報告である。 上記製剤の製造工程には、冷アルコール分画工程、ウイルス除去膜ろ過工程、加熱工程等の原理の異なるウイルスクリアランス工程が導入されており、各工程のウイルスクリアランス効果は「血漿分画製剤のウイルスに対する安全性確保に関するガイドライン（医薬発第 1047 号、平成 11 年 8 月 30 日）」に基づく、モデルウイルスを用いたウイルスプロセスバリデーションにより確認されている。今回報告した新種のコロナウイルスのモデルウイルスには、エンベロープの有無、核酸の種類等から、ウシウイルス性下痢ウイルス（BVDV）が該当すると考えられるが、上記工程の BVDV クリアランス効果については上記バリデーションにより確認されている。また、これまでに上記製剤による新規なコロナウイルスへの感染報告例は無い。 以上の点から、上記製剤はコロナウイルス感染に対する安全性を確保していると考える。

*：現在製造を行っていない

INF2013-003

World Health Organization

Global Alert and Response (GAR)

Novel coronavirus summary and literature update – as of 17 May 2013

Since April 2012, there have been 40 laboratory-confirmed cases of human infection with novel coronavirus (nCoV). Several countries in the Middle East have been affected, including Jordan, Saudi Arabia, the United Arab Emirates (UAE), and Qatar. Cases have also been reported by three countries in Europe: France, Germany, and the United Kingdom. All of the European cases have had a direct or indirect connection to the Middle East. However, in France and the United Kingdom, there has been limited local transmission among close contacts who had not been to the Middle East but had been in contact with a traveler recently returned from the Middle East.

The most recent case reported had onset on 10 May 2013. Most patients are male (79%; 31 of 39 cases with sex reported), and range in age from 24 to 94 years (median 56 years). All of the laboratory confirmed cases had respiratory disease as part of the illness, and most had severe acute respiratory disease requiring hospitalization. Reported clinical features include acute respiratory distress syndrome (ARDS), renal failure requiring hemodialysis, consumptive coagulopathy, and pericarditis. Many patients have also had gastrointestinal symptoms including diarrhea during the course of their illness. One patient, who was immunocompromised, presented with fever, diarrhea and abdominal pain, but had no respiratory symptoms initially; pneumonia was identified incidentally on a radiograph. 20 of the 40 patients have died.

Since 6 April 2013, 21 cases of infection have been confirmed and reported in the region of Al-Ahsa in the Eastern Province of Saudi Arabia (16 males and 5 females, median age 56 years). Nine of these have died, and six remain critically ill. Most patients were reported to have at least one comorbidity. The majority of the initial cases were associated with a single health care facility in Al-Ahsa. Additional cases have subsequently been identified who were not patients at the facility. Three family members of cases linked to the facility and two health care workers not associated with the Al-Ahsa facility but who had contact with laboratory confirmed cases have become infected. Two additional cases have been identified in the community that did not have any links with other cases from the Al-Ahsa healthcare facility. Although investigations are still ongoing into the source of this outbreak, early information indicated that only a small minority of these cases had contact with animals in the time leading up to their illness.

Since 8 May 2013, two cases have been reported by France. The first case became ill after a 9 day vacation to Dubai, UAE. The second case, reported on 12 May, is a patient who shared a room at a health care facility with the first case. Investigations to look for additional cases among fellow travelers of the first case and close contacts of both cases are currently underway,

Coronavirus infections

More on coronavirus infections

but no further cases have been identified. Of note, the patient's initial nasopharyngeal swab was negative, but a bronchoalveolar lavage was found to be positive for nCoV.

All clusters reported to date have occurred among family contacts or in a health care setting. Human-to-human transmission occurred in at least some of these clusters, however, the exact mode of transmission is unknown. So far, no evidence of sustained transmission beyond the clusters into the community has been observed.

Recent peer-reviewed papers published since the last update

The Coronavirus Study Group of the International Committee on Taxonomy of Viruses has published a proposed new designation for the novel coronavirus, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Reference: De Groot RJ, et al. Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Announcement of the Coronavirus Study Group. *J Virol.* Published ahead of print 15 May 2013. doi:10.1128/JVI.01244-13.

Summary assessment

The nCoV is thought to be of animal origin and to be sporadically transmitted to humans through an as yet unknown route. However, it is clear that the virus can also be transmitted between humans. So far, human-to-human transmission has only been observed in health care facilities and close family contacts and sustained transmission in the community has not been observed. The continued appearance of cases that are not part of larger clusters, and who do not have a history of animal contact, increases concerns about possible community transmission. This possibility is being investigated by authorities in Saudi Arabia.

The infection of two health care workers who had contact with infected patients and other examples of nosocomial transmission re-emphasize the need for meticulous adherence to appropriate infection control measures when nCoV is suspected, beginning with initial patient triage. Current infection control recommendations can be found at: http://www.who.int/csr/disease/coronavirus_infections/en/.

The large number of cases with reported co-morbidities suggests that increased susceptibility from underlying medical conditions may play a role in transmission. In addition, it has now been demonstrated that nCoV infection may present atypically, and initially without respiratory symptoms, in immunocompromised individuals.

Limited evidence suggests that the use of nasopharyngeal swabs for diagnosis may not be as sensitive as the use of lower respiratory specimens. Lower respiratory specimens should be used for diagnosis in addition to nasopharyngeal swabs when they are available. If an nasopharyngeal swab tests negative, consider retesting using lower respiratory specimens such as sputum, endotracheal aspirate, or bronchoalveolar lavage. Clinicians should take care to follow strict infection prevention and control guidelines when collecting respiratory specimens of any kind.

The recent increase in cases may in part be related to increased awareness among the medical community, however the demonstrated ability of this virus to transmit between humans and to cause large

outbreaks, has increased concerns about the possibility of sustained transmission. Countries in the Middle East in particular should maintain a high level of vigilance and a low threshold for testing of suspect cases. Current surveillance recommendations can be found at: http://www.who.int/csr/disease/coronavirus_infections/en/.

WHO expects that more cases will be identified. Control of the disease will require urgent multisectoral investigations aimed at identifying the source of the virus and the exposures that result in infection. It is critical for member states to report these cases and related information urgently to WHO, as required by the International Health Regulations, to inform effective international alertness, preparedness and response.

医薬品　研究報告　調査報告書

識別番号・報告回数		第1報	報告日	第一報入手日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	1. 加熱人血漿たん白（6343422）		研究報告の公表状況	Cauchemez S, et al. Transmission scenarios for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and how to tell them apart. Eurosurveillance 2013; 18(24): 1-7 WHO [Internet]. Geneva. MERS-CoV summary and literature update - as of 09July2013. Available from http://www.who.int/csr/disease/coronavirus_infections/update_20130709/en/index.html	公表国 サウジアラビア	
販売名（企業名）	1. プラズマプロテインフラクション（634342204）（Baxter）					

研究報告の概要

2012年9月に初の中東呼吸器症候群コロナウイルス（MERS-CoV）感染によるヒト肺炎例が初めてWHOへ報告されて以来、2013年7月9日時点で、同ウイルス感染の検査確定症例は80例を数えた。同時点で死亡数45例（56%）と、致死率は高い。2012年4月以降の発症について確定例が報告されたのは、サウジアラビア、ヨルダン、カタール、アラブ首長国連邦、イギリス、フランス、ドイツ、イタリアおよびチュニジアである。
コロナウイルスはエンベロープを有するウイルスであり、一本鎖RNAをゲノムとする。哺乳類及び鳥類にさまざまな疾患を起こし、コロナウイルス科には、ウシやブタの下痢やマウスの肝炎、ニワトリの伝染性気管支炎の原因ウイルス等が含まれる。MERS-CoVは、2003年に流行したSARSコロナウイルスと同じベータコロナウイルス属に分類される。
MERS-CoV感染の起源はサウジアラビアであるとされており、感染源や感染経路に関しては未知である。動物の感染例に関する報告は少なく、宿主生物は特定されていない。しかしながら、アラビア半島で発生した何症例かは、感染動物への曝露による感染であると推察された。欧州および北アフリカにおける患者は、直接あるいは間接的な中東からの輸入例であるとされていたが、イギリス、フランスおよびチュニジアにおいては、患者との濃厚接触者に検査確定例が発生した。サウジアラビアおよびヨルダンにおいても、家族内あるいは医療機関内におけるヒト-ヒト感染が疑われる患者クラスターがあった。
これまでに報告されたヒト感染例は、限定的なヒト-ヒト感染のみを示唆しており、持続するヒト-ヒト感染の証拠はない。しかし、サウジアラビアの医療従事者および検査確定症例と接触した小児に、無症候性のMERS-CoV感染例が報告された。したがって、他にも報告されていない感染例が存在する余地があり、既に持続するヒト-ヒト感染が起こっている可能性も示唆される。SARSの再来と危惧する声もあり、継続したモニタリングと徹底した疫学的分析が求められる。

報告企業の意見	今後の対応
感染源や感染経路は不明であり、これまでに継続するヒト-ヒト感染、特に血液を介したヒト間感染を裏付けるの証拠は得られていない。 以上により、現段階で特段の安全確保措置は不要であると判断した。	今後とも注意深く同感染症の発生数や頻度の変化、発生地域の拡大等の動向について情報収集に努める。

使用上の注意記載状況・その他参考事項等

プラズマプロテインフラクション：該当ロットなし

［使用上の注意記載状況］
プラズマプロテインフラクション：重要な基本的注意［患者への説明］（本剤の使用にあたっては、疾病の治療における本剤の必要性とともに、本剤の製造に際し感染症の伝播を防止するための安全対策が講じられているが、ヒト血漿を原料としていることに由来する感染症伝播のリスクを完全に排除することができないことを、患者に対して説明し、理解を得るよう努めること。）
ヘモフィルM：一般的注意（非A非B型肝炎等のウイルス感染症の危険性を完全に否定出来ないので、観察を十分に行い、肝障害があらわれた場合には適切な処置を行うこと。）

文献番号 8・9

PERSPECTIVES

Transmission scenarios for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and how to tell them apart

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Detection of human cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection internationally is a global public health concern. Rigorous risk assessment is particularly challenging in a context where surveillance may be subject to under-ascertainment and a selection bias towards more severe cases. We would like to assess whether the virus is capable of causing widespread human epidemics, and whether self-sustaining transmission is already under way. Here we review possible transmission scenarios for MERS-CoV and their implications for risk assessment and control. We discuss how existing data, future investigations and analyses may help in reducing uncertainty and refining the public health risk assessment and present analytical approaches that allow robust assessment of epidemiological characteristics, even from partial and biased surveillance data. Finally, we urge that adequate data be collected on future cases to permit rigorous assessment of the transmission characteristics and severity of MERS-CoV, and the public health threat it may pose. Going beyond minimal case reporting, open international collaboration, under the guidance of the World Health Organization and the International Health Regulations, will impact on how this potential epidemic unfolds and prospects for control.

As of 30 May 2013, 50 laboratory-confirmed cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection have occurred worldwide [1]. An apparently high case-fatality ratio (60%; 30 deaths as of 30 May 2013 [1]) and growing evidence that human-to-human transmission is occurring [2] make MERS-CoV a threat to global health. The current situation has already been compared to the early stages of the severe acute respiratory syndrome (SARS) epidemic in 2003 [3,4].

No animal reservoir has yet been identified for MERS-CoV, and yet human cases, mostly severe, have been detected over a wide geographical area in the Middle East and Europe. If most human cases to date have arisen from animal exposure, this implies a large but as yet uncharacterised zoonotic epidemic is under way in animal species to which humans have frequent exposure (Figure 1A). In this scenario, we might expect relatively small numbers of human cases overall, though with the limited surveillance data available to date, we cannot rule out the possibility that substantial numbers of human cases, with milder disease, have gone undetected.

Even if most human cases to date have been infected through zoonotic exposure, is it possible that MERS-CoV already has the potential to support sustained human-to-human transmission but has by chance so far failed to do so?

Alternatively, how feasible is it that most of the severe MERS-CoV cases detected to date were in fact infected via human-to-human transmission and that the epidemic is already self-sustaining in human populations (Figure 1B)? Under this transmission scenario, substantial numbers of human infections may have already occurred, with only a small proportion of them being detected. But is it feasible that such an epidemic would not have been recognised?

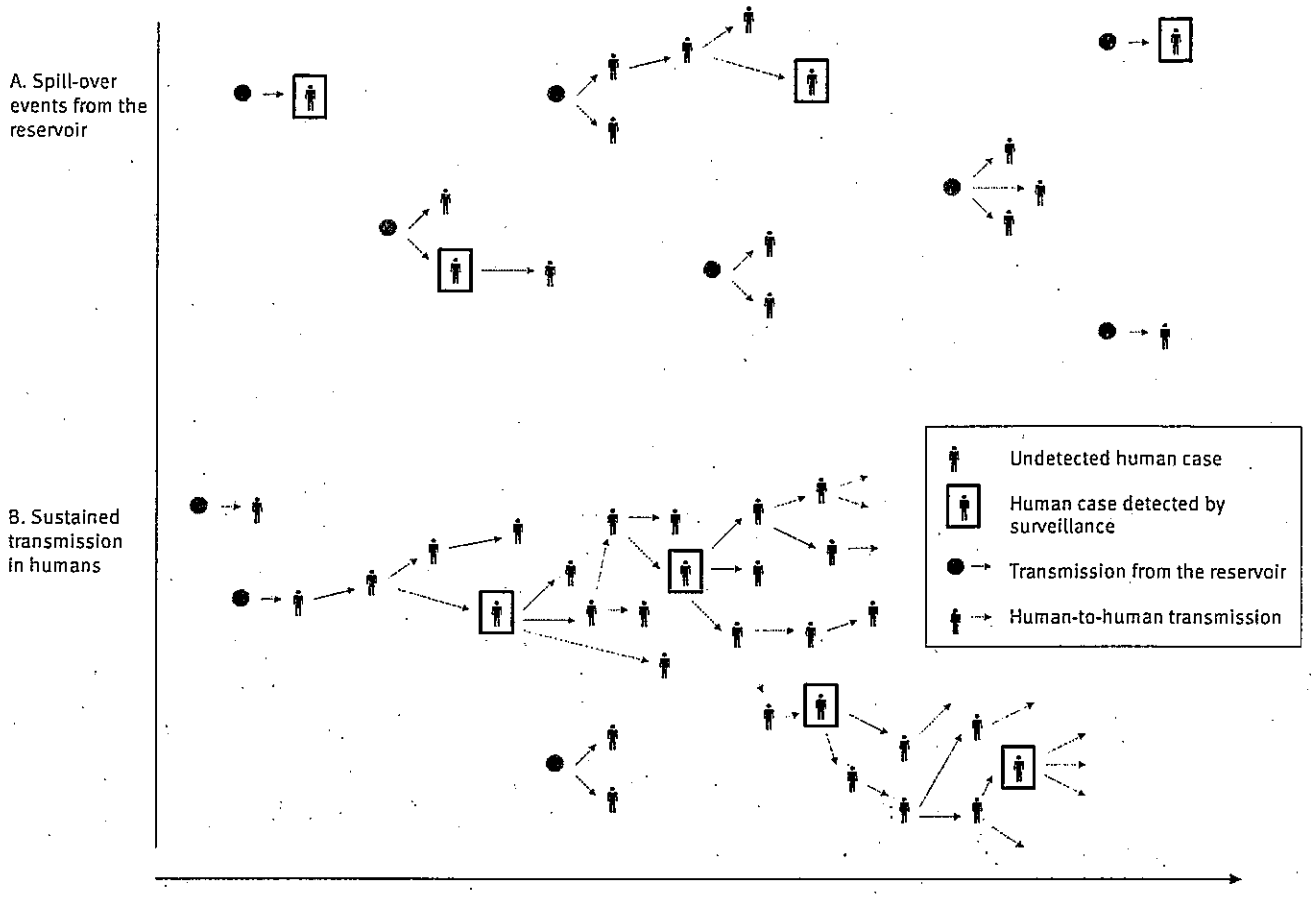
Each of these scenarios has very different implications for the assessment of severity, relevance of reservoir-targeted strategies and potential impact of MERS-CoV globally. Although it may not be possible to completely rule out any of the scenarios with the data currently available, it is timely to consider the priorities for data collection and analysis as cases accrue, so as to best be able to reduce uncertainty and refine the public health risk assessment.

Transmission scenarios for an emerging infection

The human-to-human transmissibility (and thus epidemic potential) of an emerging pathogen is quantified by the (effective) reproduction number, *R*, the average number of secondary infections caused by an index

FIGURE 1

Two illustrative scenarios for transmission of Middle East Respiratory Syndrome Coronavirus (MERS-CoV)



A. Few human-to-human infection events have occurred and observed clusters have arisen from separate spill-over events (i.e. introductions from the animal reservoir into human populations).

B. Many undetected human-to-human transmission events have occurred and the epidemic is already self-sustaining.

human infection. Depending on the value of R, different transmission scenarios are possible, as described below.

Scenario 1: subcritical outbreaks ($R<1$)

If $R<1$, a single spill-over event from a reservoir into human populations may generate a cluster of cases via human-to-human transmission, but cannot generate a disseminated, self-sustaining epidemic in humans. The number of human infections expected under this scenario is roughly proportional to the number of zoonotic introductions of the virus into the human population, with a multiplier, $1/(1-R)$, that increases with R (twofold if $R=0.5$, but 10-fold if $R=0.9$).

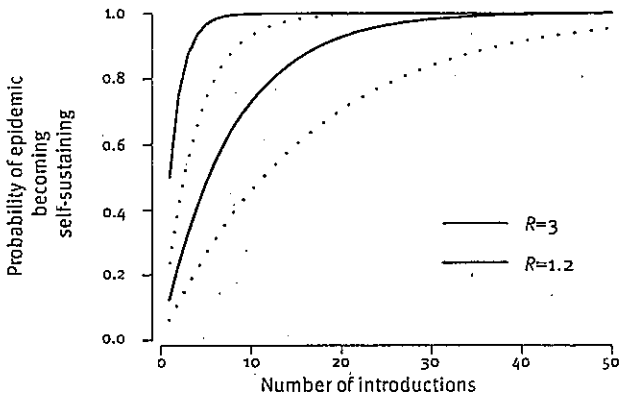
In this scenario, human infections can be mitigated by controlling the epidemic in the reservoir and/or preventing human exposure to the reservoir. Examples of this scenario are A(H5N1) and A(H7N9) avian influenzas.

Scenario 2: supercritical outbreaks ($R>1$ but epidemic has not yet become self-sustaining in human populations)

If $R>1$, a self-sustaining epidemic in humans is possible but emergence following introduction is a chance event: many chains of transmission may extinguish themselves by chance, especially if R is close to 1. In the case of SARS, for example, where 'super-spreading' events played an important role in transmission (i.e. a small proportion of cases were responsible for a large proportion of onward transmission), it has been estimated that there was only a 24% probability that a single introduction would generate a self-sustaining epidemic [5] (following [5], we technically define 'super-spreading' events by an over-dispersion parameter $k=0.16$; the absence of super-spreading events is defined by $k=0.5$). This is because if the first cases were not part of a super-spreading event, they would be unlikely to generate further cases. However,

FIGURE 2

Probability that the epidemic has become self-sustaining in humans after n introductions from the reservoir if $R>1$



R: reproduction number.

This probability depends not only on *R* but also on the presence of super- spreading events (SSE) (without SSE: plain line; with SSE: dotted line). Values $R=3$ and $R=1.2$ were selected for illustrative purposes.

in this scenario, a self-sustaining epidemic is eventually inevitable if zoonotic introductions into the human population continue (Figure 2). As with the subcritical scenario (R<1), reducing infections from the reservoir is critical to reducing the public health risk.

Scenario 3: self-sustaining epidemic ($R>1$)

If $R>1$ and the epidemic has become self-sustaining in humans, the number of human cases is expected to grow exponentially over time. The rate of growth increases with R, but decreases with the mean generation time (GT), the time lag from infection of an index case to infection of those they infect. For example, for an eight-day GT – similar to that of SARS – once self-sustaining, the number of human cases is expected to double about every week if $R=2$, but only about every month if $R=1.2$. Although chance effects may mask exponential growth early in the epidemic, a clear signal of increasing incidence would be expected once the number of prevalent infections increases sufficiently [6]. If case ascertainment remains constant over time, the incidence of detected cases would be expected to track that of underlying infections, even if only a small proportion of cases are detected. Once the epidemic is self-sustaining, control of the epidemic in the reservoir would have limited impact on the epidemic in humans.

Publicly available data

As of 30 May 2013, 50 confirmed cases of MERS-CoV have been reported with symptom onset since April 2012 from Saudi Arabia, Jordan, Qatar, United Arab Emirates, the United Kingdom (UK), France and Tunisia [1,2,7-24]. There are additional probable cases from Jordan, Saudi Arabia and Tunisia [1,12,14]. Information on animal exposures is limited and the animal reservoir has not yet been identified. However, we suspect that some of the cases may have arisen from zoonotic exposure in the Arabian Peninsula. Human-to-human transmission is suspected in several familial and healthcare facility clusters in Saudi Arabia, Jordan UK and France. We understand that follow-up investigations of contacts of the confirmed MERS-CoV cases have taken place by Ministry of Health officials in affected countries, finding no evidence of additional symptomatic infection [7-10,15-19]. At this stage, it is difficult to ascertain whether other primary zoonotic or secondary human-to-human cases have been missed. Most cases have been reported as severe disease (40 of 44 with documented severity) and 30 (as of 30 May 2013) have been fatal [25]. Table 1 summarises data for each cluster.

Urgent data needs

Existing and additional data will help characterise the MERS-CoV transmission scenario. Many appeals for data have been brought forward by several experts and institutions such as the World Health Organization (WHO). We support this and summarise data requirements and the studies required to collect such data are summarised in Table 2. We illustrate here how these data may be analysed and interpreted with adequate statistical techniques [26-28].

Line-list data on confirmed cases

The spatio-temporal dynamics of cases may be used to ascertain whether the epidemic is self-sustaining and if so, to characterise human-to-human transmission [27-29]. It is therefore important that detailed epidemiological information is recorded for all confirmed and probable cases.

Identification of the reservoir species and exposure data

The importance of identifying animal reservoir(s) and understanding human exposure to reservoir species (e.g. direct contact, contact via contaminated food) is well recognised. Once the reservoir has been identified, any exposure of MERS-CoV human cases to that reservoir should be documented in epidemiological investigations. Currently, the uncertainty regarding reservoirs and modes of transmission mean that only five of 50 cases can reliably be classified as 'human-to-human' transmission, with the source of infection unclear for the remainder.

If none of the MERS-CoV cases detected by routine surveillance had exposure to the reservoir(s), this would clearly indicate that an epidemic in humans is already self-sustaining [26]. By contrast, if a substantial proportion of cases have been exposed to the reservoir(s), it may be possible to rule out the hypothesis that $R\geq1$.

TABLE 1

Summary information per cluster of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection, as of 30 May 2013

Cluster ID	Country identified	Date of reporting	Date first symptom onset	Number of confirmed cases	Number of cases infected by human-to-human transmission	Number of reported probable cases	References
1	Saudia Arabia	20 Sep 2012	13 Jun 2012	1	0	0	[1,19]
2	Saudia Arabia	1 Nov 2012	5 Oct 2012	3	0	1	[1,13]
3	Saudia Arabia	4 Nov 2012	9 Oct 2012	1	0	0	[7,21]
4	Jordan	30 Nov 2012	21 Mar 12	2	0	9	[1,12]
5	United Kingdom	22 Sep 2012	3 Sep 2012	1	0	0	[8]
6	Germany	1 Nov 2012	1 Oct 2012	1	0	0	[1,9]
7	United Kingdom	11 Feb 2013	24 Jan 2013	3	2	0	[1,2]
8	Saudia Arabia	21 Feb 2013	NR	1	0	0	[1]
9	Saudia Arabia	7 Mar 2013	NR	1	0	0	[1]
10	Saudia Arabia	12 Mar 2013	24 Feb 2013	2	0	0	[1]
11	Germany	26 Mar 2013	NR	1	0	0	[1]
12	Saudia Arabia	9 May 2013	6 Apr 2013	21	Unknown	0	[20,22-24]
13	France	9 May 2013	22 Apr 2013	2	0	0	[1,11]
14	Saudia Arabia	14 May 2013	25 Apr 2013	1	0	0	[1]
15	Saudia Arabia	18 May 2013	28 Apr 2013	1	0	0	[1]
16	Tunisia	22 May 2013	NR	2	2	1	[1]
17	Saudia Arabia	22 May 2013	NR	1	0	0	[1]
18	Saudia Arabia	28 May 2013	12 May 2013	5	Unknown	0	[1]

NR: not reported.

A similar analytical approach can be used to assess local levels of transmission in countries where MERS-CoV cases are imported from abroad. We can determine if there is self-sustaining transmission in a country by monitoring the proportion of cases detected by routine surveillance with a travel history to other affected countries [26].

If reservoir exposure cannot be found in spite of detailed epidemiological investigations, this may indicate that the epidemic is already self-sustaining in humans. It is therefore important that efforts to identify the reservoir are documented even if they are unsuccessful. To date, very few of the 50 cases have reported contact with animals [1].

Thorough epidemiological investigations of clusters of human cases

Thorough and systematic epidemiological investigations – including contact tracing of all household, familial, social and occupational contacts, with virological and immunological testing – permits assessment of the extent of human infection with MERS-CoV among contacts of confirmed cases [29]. In this context, virological and serological testing is important for ascertaining secondary infections.

As stated above, if $R>1$, human-to-human transmission will eventually become self-sustaining after a sufficiently large number of virus introductions. So, if thorough cluster investigations indicate that all introductions to date have failed to generate large outbreaks, we can derive an upper bound for R (Figure 3). The distribution of cluster sizes can also be used to estimate R [30,31].

Routine surveillance is likely to be biased towards severe cases. As a consequence, the case-fatality ratio estimated from cases detected by routine surveillance may be a substantial overestimate. Secondary cases detected during thorough epidemiological investigations of human clusters are expected to constitute a more representative sample of cases in general, meaning more reliable estimates of severity will be obtained by recording clinical outcomes in this subset of cases. Seroepidemiological studies allow for better characterisation of the spectrum of disease, and for the calculation of the proportion of asymptomatic or subclinical infections [29].

Population-level data

Once reliable serological assays are available to measure levels of antibodies to MERS-CoV, it will be

TABLE 2

Assessing the transmission scenario of a zoonotic virus: data requirements, suggested investigations, parameter estimation and policy implications

Improved knowledge	Data requirements	Recommended study investigations	Parameter estimation	Policy implications
Identification of reservoir species and exposure data	• Identification of the source of infection, of animal reservoir specie(s) and of amplifier specie(s) • Exposure history of confirmed and probable cases	• Animal studies • Detailed exposure history collected during initial investigations of suspected cases	• Test if $R>1$	• Mitigation measures can be implemented to reduce transmission from the source to humans • Determine if epidemic is self-sustaining in humans
Thorough epidemiological investigations of clusters of human cases[b]	• Data as above, plus • Detailed epidemiological investigations of all cases to determine cluster size	Epidemiological, virological and serological[a] investigations of: • close familial, social and occupational contacts of MERS-CoV confirmed and probable cases • healthcare workers caring for MERS-CoV patients	• Estimate R • Estimate the generation time • Estimate severity parameters	• Make an assessment of severity • Determine if epidemic is self-sustaining in humans • Guide efforts for prevention of (human-to-human) transmission
Population-level infection data[b]	• Estimates of population-level seroprevalence	• Community-based seroepidemiological[a] studies	• Estimate the extent of infection in humans	• Identify risk groups for targeted mitigation measures to reduce transmission

MERS-CoV: Middle East Respiratory Syndrome Coronavirus.

[a] The development of serological testing is currently limited, though actively being developed.

[b] Protocols for epidemiological investigations can be found at [34,35].

important to undertake serological surveys in communities affected early to assess the prevalence of MERS-CoV infection. Should MERS-CoV cases continue to arise in those communities, a rapid follow-up study to collect paired serum samples would be highly valuable. Even a relatively small number of paired sera (about 1,000) could be used to estimate underlying infection rates and refine estimates of severity [32].

Conclusions

We have described three possible transmission scenarios for the emergence of a novel human pathogen from a suspected zoonotic reservoir, with different implications for risk assessment and control.

The most optimistic scenario is that $R<1$, and thus there is no immediate threat of a large-scale human epidemic. In this scenario, identifying the reservoir will inform efforts to limit human exposure. Detailed genetic investigations and estimation of R are also important for determining the selection pressure and opportunity for the virus to evolve higher human transmissibility [33].

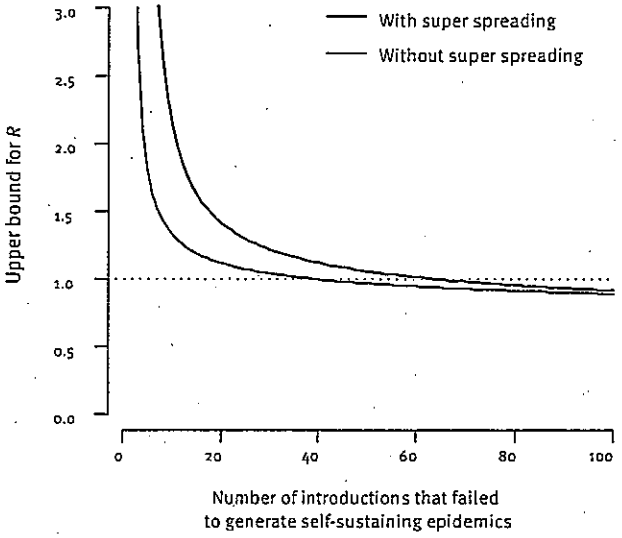
If $R>1$ but by chance MERS-CoV has not yet generated a self-sustaining epidemic, the total number of animal-to-human infections must have been relatively small. This would suggest that the severe cases that have been detected are not the tip of the iceberg and that disease severity is therefore high.

The final possibility is that $R>1$ and that human-to-human transmission is already self-sustaining. If this is the case, R must still be relatively low (i.e. <2) unless transmission only began to be self-sustaining in the recent past (e.g. early 2013). In this scenario, overall human case numbers might already be relatively large, suggesting that severity may be substantially lower than it appears from current case reports. Rapid implementation of infection control measures upon detection of MERS-CoV cases may be limiting onward spread beyond close contacts, and may explain the lack of clear-cut evidence from the epidemiological data available thus far that human-to-human transmission is self-sustaining.

Given the current level of uncertainty around MERS-CoV, it is important that adequate data are collected on future cases to underpin rigorous assessment of the transmission characteristics and severity of MERS-CoV, and the public health threat it may pose. This paper has reviewed the epidemiological investigations needed (Table 2); use of standard protocols – being developed by several groups; see available protocols

FIGURE 3

Upper bound for the reproduction number R as a function of the number of introductions from the reservoir that failed to generate self-sustaining epidemics



from WHO [34], the Consortium for the Standardization of Influenza Seroepidemiology (CONSISE) [35] and International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) [36]) – where possible, would be beneficial. Going beyond minimal case reporting, open international collaboration, guided by the International Health Regulations, will impact how this potential epidemic unfolds and prospects for control.

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Conflict of interest

SC received consulting fees from Sanofi Pasteur MSD for a project on the modelling of varicella zoster virus transmission. The authors declare no other competing interests.

Authors' contributions

SC, MVK, SR, SAD, CF, NMF planned the analysis; MVK compiled the data; SC developed the methods and ran the analysis; SC wrote the first draft; SC, MVK, SR, SAD, CF, NMF edited the paper.

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World Health Organization

Global Alert and Response (GAR)

MERS-CoV summary and literature update – as of 09 July 2013

Since April 2012, 80 laboratory-confirmed cases of human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported to WHO. Forty-five of the confirmed cases have died (56%). Forty-nine of 75 cases (65%) for which the sex is known were male and the median age of the cases with known age is 51 years (range, 14 months to 94 years). Affected countries in the Middle East include Jordan, Qatar, Saudi Arabia and the United Arab Emirates (UAE); in Europe countries affected include France, Germany, the United Kingdom (UK) and Italy; and in North Africa, Tunisia. No new countries have reported MERS-CoV cases since the last update. All the European and North African cases have had a direct or indirect connection to the Middle East. However, in France, Italy, Tunisia and UK, there has been limited local transmission among close contacts that had not been to the Middle East.

Since the last update, 16 new laboratory-confirmed cases of MERS-CoV were reported by Saudi Arabia. Eight of the new cases were reported to be asymptomatic. Of the eight asymptomatic cases four were female health care workers, two from the Ta'if governorate and two from the Eastern Province of Saudi Arabia. The other four asymptomatic cases were children aged 7 to 15 years from Riyadh and the Eastern Province of Saudi Arabia who had contact with confirmed cases. For further details regarding the cases see Disease Outbreak News.

WHO MERS-CoV related activities and upcoming guidance

WHO is currently preparing travel and health advice for travellers to forthcoming mass gatherings.

Recommendations for infection prevention and control for MERS-CoV patients in hospital are under review. Advice on infection prevention for patients being cared for at home is under development.

WHO is convening an Emergency Committee meeting, as described in the International Health Regulations (2005), to review the current MERS-CoV outbreak, discuss whether the outbreak constitutes a Public Health Emergency of International Concern (PHEIC), and advise the Director General on temporary recommendations for any necessary public health actions.

WHO is also coordinating the collection of a panel of clinical serum specimens, which will include both MERS-CoV positive and negative specimens, to standardize serological assays. This activity is being done in

Coronavirus infections

More on coronavirus infections

collaboration with an international network of public health and research laboratories.

Recent guidelines

On 5 July, WHO published a guideline for investigation of MERS-CoV cases. It provides recommendations for early case investigation including further case finding, surveillance enhancements, and studies that need to be done around new cases.

On 3 July, WHO published revised case definitions for MERS-CoV confirmed and probable cases based on new epidemiological and clinical information. The document also contains recommendations on further evaluation for cases with inconclusive tests and asymptomatic infections.

On 27 June, WHO published interim surveillance recommendations for human infection with MERS-CoV. The two major changes include a stronger recommendation for the use of lower respiratory tract specimens in addition to nasopharyngeal swabs for diagnostic testing and a longer observation period for contacts of cases.

Recent papers in the scientific literature

Several MERS-CoV scientific investigations have been published in journals:

- The Saudi Arabian Ministry of Health provided an in-depth analysis of 25 (23 confirmed and 2 probable) MERS-CoV cases associated with an outbreak in Al-Hasa region of Saudi Arabia. The outbreak involved patients, their family members and health care workers from four different hospitals, including a haemodialysis unit, an intensive care unit and other inpatient units. Human-to-human-transmission was considered the likely source of infection for most of the cases. The estimated median incubation period was 5.2 days (95% confidence interval 1.9 to 14.7 days).
Reference: Assiri A et al. Hospital outbreak of Middle East Respiratory Syndrome coronavirus. *New England Journal of Medecine*. Published online 19 June 2013. DOI: 10.1056/NEJMoa1306742 http://www.nejm.org/doi/pdf/10.1056/NEJMoa1306742

- German investigators published a viral load profile of a patient infected with MERS-CoV treated in Germany in March 2013. They found very high viral loads in lower respiratory tract samples from the patient compared with upper respiratory samples, and low concentrations of the virus in stool, urine and blood.
Reference: Drosten C et al. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. *Lancet*. Published Online 17 June 2013. http://dx.doi.org/10.1016/S1473-3099(13)70154-3

- A recent paper describes three possible transmission scenarios for MERS-CoV, detailing the implications for risk assessment and control for each. The scenarios include subcritical outbreaks where the reproduction number (R0) is less than 1, supercritical outbreaks where R0 is greater than 1 but the epidemic has not become self-sustaining in human populations, and a self-sustaining epidemic where R0 is greater than one. The authors stress the importance of adequate data collection in order to permit rigorous

assessment of the severity and transmission characteristics of MERS-CoV.
Reference: Cauchemez S et al. Transmission scenarios for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and how to tell them apart. *Euro Surveillance*. Published online 13 June 2013.
http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20503

Summary assessment

With recent reports of asymptomatic and mild cases, the proportion of confirmed cases that have died of MERS-CoV infections is lower than previously reported, as is the average age, and the proportion of patients who are female has increased. It is noteworthy that these cases have been detected as part of contact investigations around severe cases. These severe cases were discovered as a result of surveillance activities that focus on finding severely affected patients. Index cases, the first cases occurring in a cluster, presumably are more likely to have had a non-human exposure as their source of infection and continue to be predominantly older males, perhaps providing a clue to the exposure that resulted in their infection. Whether the relative mildness of illness in contact cases is an artifact of surveillance and case-finding activities or represents a difference in virulence between sporadic infections acquired from non-human exposures and those acquired from human-to-human transmission is unknown.

The recent mild and asymptomatic cases raise concerns about the possibility of large numbers of milder cases going undetected. While it is clear that human-to-human transmission does occur, it is not clear whether transmission is sustained in the community. The currently observed pattern of disease occurrence could be consistent either with ongoing transmission in an animal reservoir with sporadic spillover into humans resulting in non-sustained clusters, or unrecognized sustained transmission among humans with occasional severe cases. Detailed case contact investigations, increased surveillance in other countries of the region, and formal studies of non-human exposures of index cases are urgently needed to answer these questions. A new guideline for these case investigations has recently been published (see above).

The public health importance of asymptomatic cases is uncertain. More information is needed about the virus excretion patterns in persons without symptoms to understand the risk they may pose to non-infected persons. Experience from the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 suggests that very little if any transmission occurred from asymptomatic individuals. In addition, in the absence of symptomatic illness, the burden of proof must be higher because of the possibility of misclassification from false positive tests that result from laboratory contamination. In most viral infections, an immunological response, such as development of specific antibodies, would be expected even with mild or asymptomatic infection; as such, serological testing may be useful as additional confirmation of the diagnosis. Additional steps to reconfirm asymptomatic cases, or any case in which the diagnosis is suspect, could also include re-extraction of RNA from the original clinical specimen and testing for different virus target genes, ideally in an independent laboratory.
http://www.who.int/csr/disease/coronavirus_infections/LaboratoryTestingNovelCoronavirus_21Dec12.pdf

WHO continues to request that Member States report all confirmed and probable cases along with information about their exposures, testing, and

clinical course to inform the most effective international preparedness and response. WHO strongly recommends detailed case investigations for every case, case-control-studies for index cases and intensive follow up of contacts with serological testing to improve knowledge of critical features of the MERS-CoV infection.

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医薬部外品　　研究報告　調査報告書
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研究報告の概要

はじめに
テンブスウイルス（TMUV）は蚊が媒介するフラビウイルスで、マレーシアにおいて 1970 年代にイエカ属の蚊から最初に分離された（Platt ら、1975 年）が、TMUV 感染に関連した疾患は知られていなかった。しかし、最初に Sitiawan ウイルスと名付けたヒヨコ起源の TMUV 分離株は、脳炎を引き起こし、ブロイラーのヒヨコの成長を遅らせた（Kono ら、2000 年）。
2010 年に中国で、TMUV はアヒルで深刻な産卵低下を引き起こしていることが分かった。卵巣での充血、出血、変性、歪み及びリンパ球浸潤は、殆ど全ての病気に罹ったアヒルに一貫して観察された主要な病理学的変化であった。変化に基づいて、疾患は TMUV によって引き起こされたアヒル出血性卵巣炎（DHO）と診断された。最近の研究は、TMUV は自然界に広く分布し、種々のアヒル（北京ダック、桜渓谷北京ダックや紹興ダック、縉雲ダック、竜岩ダック、金鼎ダックやカーキキャンベルダックを含む）で存在することを示す。中国における DHO の発生から 2 年間で報告されたアヒルや鶏からの TMUV の 10 以上の分離株があった（Cao ら、2011 年； Su ら、2011 年； Tang ら、2012 年前半）。
アヒル TMUV 感染の我々の調査の間に、我々はヒトへの感染を引き起こす TMUV も発見した。
この報告書は、この人獣共通感染症の新たな性質をハイライトし、そしてその可能性がある公衆衛生転帰に対する注意を呼びかける。

材料と方法
サンプル収集
血清学的調査は、中国・山東省で流行した 2010 年 9 月から 2012 年 10 月の間にアヒル農場、或いは殺処分鳥（culled birds）で働いていた 132 人の間で行われた。口腔スワブも、ウイルス検出のために同時に収集された。サンプルは semi-nested 逆転写 PCR（SN-RT-PCR）と IgG ELISA を用いて TMUV の存在をスクリーニングされた。許可は採血前に与えられ、スワブサンプルはアヒル殺処分者と農場労働者から採取された。山東農業大学の研究倫理委員会は、この調査を承認した。

ELISA 法
我々は、ELISA 法を用いて血清中の TMUV 特異抗体を検出した。簡単に説明すると、TMUV E の発現タンパク質を精製し、一晩 4℃で培養することによってウェル（50ng/well）上にコーティングした。ウェルは pH7.4 のリン酸緩衝食塩液（PBS）と 0.05% Tween20 洗浄緩衝液で 3 回洗浄した。それから、50μL のブロッキング緩衝液（PBS、0.05%の Tween20 と 2.5%のウシ血清アルブミン）を各ウェルに添加し、全ての結びついていない部位を飽和するために 37℃で 1 時間培養した。コーティングしたプレートは PBS と 0.05%の Tween20 で 3 回洗浄した。100 倍希釈した血清サンプルは 100μL/well 添加し、37℃で 1 時間培養した。培養と上述した 3 回洗浄サイクルの後、ヤギ抗ヒト IgG で標識した西洋ワサビ過酸化酵素（HRP）の 5000 倍希釈液を 100μL/well 添加し、そしてプレートは 37℃で 1 時間培養し、その後洗浄緩衝液で 3 回洗浄した。pH5.0 の 0.05M リン酸-クエン酸緩衝液中に 0.04%のオルトフェニレンジアミンと 0.04%の H_2O_2 を含む 100μL 容量の基質溶液を添加した。反応は室温で 30 分間行った。発色現象は各ウェルに 2.5M の H_2SO_4 を 50μL 添加することにより 10 分後に停止した。吸光度はプレートリーダーを用いて 450nm で読み取った。複製の陰性コントロールヒト血清は各プレートに含まれていた。0.689 より高い TMUV に対する IgG の ELISA 光学濃度（OD）値は陽性と考えられた。

ウイルス中和検査

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1)本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-1 抗体陰性で、かつ ALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV - 1、HBV 及び HCV について核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人ハプトグロビンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

文献番号 10

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我々は、同量で熱不活化血清サンプル（1:10－1:640）の2倍希釈した2%-ウシ胎児血清（インビトロゲン社、グランドアイランド、ニューヨーク、米国）中にTMUV株SDMSの100 $TCID_{50}$/mLを混ぜ、そして5%のCO_2中で37℃で75分間混合物を培養した。次いで、混合物は2%-ウシ胎児血清（FCS）、100U/mLのペニシリン及び100μg/mLのストレプトマイシンの入った6ウエル培養プレート（コーニング社、ニューヨーク、米国USA）中で増殖させたベロ細胞上に接種した。細胞培養は72時間、5%のCO_2中で37℃で培養した。1ウエルの細胞が10%以下の細胞変性を示した場合、サンプルはTMUV中和抗体の陽性と考えられた。

Semi-nested RT-PCR
132人からの口腔スワブサンプルは、NS3基準のsemi-nested RT-PCR（SN-RT-PCR）によるTMUV RNAの検出のためのRNA抽出（TIANGEN社、北京、中国）に使われた。簡単に説明すると、NS3遺伝子の増幅のためのSN-RT-PCRの初回ラウンドは、NS3F（5'-ATGGATGAAGCYCATTTY CAC-3'）
及びNS3R（5'-CCAAGTTGGCYCCCATCTC-3'）の20pmolを用いてcDNAを行った。10×EX Taq緩衝液（Mg^{2+}をプラス）の5μL、dNTP混合物（それぞれ10mMのdNTP）の1μL、5単位のEX Taqポリメラーゼ（宝酒造、大連、中国）及び1μLの鋳型cDNAを含むPCR混液は、ＲＮＡ分解酵素フリー水で50μLにした。熱循環プログラムは5分間94℃で初回変性を含み、35サイクル後に、30秒間94℃でそれぞれ変性を続け、30秒55℃でアニールと30秒間72℃で延伸し、72℃10分間最終延伸した。NS5遺伝子のためのSN-RT-PCRの第2ラウンドは、第1ラウンドと同じ条件で鋳型DNAとNS3FとSNR（5'-AGCACACGGCAATCTCAT -3'）の20pmol/μLとして初回RT-PCR生成物の1μLを用いて行った。

系統分析
系統分析は、NS3遺伝子の基礎となるヌクレオチド277に基づいた。多様な配列は、ソフトウェアBioEdit（バージョン7.0.5.2）のClustalW（Ibis Biosciences社、Carlsbad、カリフォルニア、米国）方法を使用して構築した。系統樹は1000のブートストラップ複製（田村ら、2007年）に続いて絶対距離によるMEGAプログラム（バージョン4.0）の近隣結合法を用いて描かれた。

結果と考察
我々は、中国におけるTMUVのヒト感染を示唆する。TMUV感染の流行時に収集した132人のアヒル産業労働者の血清サンプル中のTMUV抗体と口腔スワブ中のTMUV RNAを測定した。我々の知見は、TMUVのヒト感染に対する家禽のリスクが高いことを証明した。
我々の調査で、3つの診断方法はヒトにおけるTMUV感染の検出のために使われた。IgG ELISAは71.9%（95/132）の陽性率を、そしてNS3基準のSN-RT-PCRは47.7%（63/132；　表1）の陽性率を得た。アヒル農場労働者からの口腔スワブサンプルでのTMUV NS3遺伝子の系統分析は、以前に報告されたように、他のアヒルTMUV株との密接な関係を示しているNtayaウイルス群の蚊媒介性フラビウイルスに明確に定義されたグループを示した（図1；　唐ら、2012年；潤ら、2012年）。BLAST分析は、ヒトTMUVのNS3遺伝子の一部が、それぞれBYDウイルスとYY5ウイルスのものとほぼ100%ヌクレオチド同一性を有することが示された。全てのTMUV株のNS3遺伝子は、SitiawanウイルスやTMUV株MM1775のものと約85.2%と87.7%のヌクレオチド相同性を共有した。
我々の調査は、アヒルーヒト感染のリスクが高いグループの間でTMUV感染の根拠（例えば、中国山東省で2010年から2012年の間に流行した家禽への暴露）を示し、そしてヒトでのTMUV感染の意識向上、強化した前向き調査及びより現在の血清調査の必要性を示唆する。SN-RT-PCは、早期TMUV感染時に有用な診断方法であるかもしれないが、殆どのTMUV感染症例では、血清学的検査（例えば、IgG ELISA及びウイルス中和）は有用な結果をもたらす可能性が高い。公衆衛生上の理由のために、更なる調査はヒトTMUVを分離し、その疫学的、遺伝的及び病原性の特徴を調査するために行われるべきである。

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報告企業の意見	今後の対応	
テンブスウイルス（Tembusu virus：TMUV）はフラビウイルス科（Family Flavivirus）フラビウイルス属（Flavivirus）に分類される新規ウイルスである。フラビウイルスの粒子は直径 40～60nm で、脂質エンベロープを有する RNA ウイルスである。万一、原料血漿に TMUV が混入したとしても、Bovine viral diarrhoea virus（BVDV）をモデルウイルスとしたウイルスクリアランス試験結果から、本剤の製造工程において不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。	

Transboundary and Emerging Diseases

Transboundary and Emerging Diseases

RAPID COMMUNICATION

Tembusu Virus in Human, China

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Keywords:
Tembusu virus; human; ducks; *Flavivirus*; antibodies

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Summary:
Tembusu virus (TMUV) infection in ducks, geese and house sparrows was reported in China. To confirm the emergence of TMUV in humans, we investigated TMUV as a possible infection in duck industry workers in Shandong, China. Of 132 serum samples tested, 95 (71.9%) had TMUV antibodies. In oral swabs detection, 63 (47.7%) samples were positive for TMUV RNA. Nucleotide sequences of 277 bp coding the partial NS3 protein showed more than 99.5% identity with other duck TMUV strains, which can cause severe egg drop in ducks. These findings contribute to the realization that TMUV may be overlooked as a zoonotic transmission in China.

Introduction

Tembusu virus (TMUV) is a mosquito-borne flavivirus and first isolated from mosquitoes of the genus *Culex* in 1970s in Malaysia (Platt et al., 1975), but the disease associated with TMUV infection was not known. However, a chick-origin TMUV isolate, originally named Sitiawan virus, can cause encephalitis and retarded growth in broiler chicks (Kono et al., 2000).

In China in 2010, TMUV was found causing severe egg drop in ducks. Hyperaemia, haemorrhage, degeneration, distortion and lymphocyte infiltration in the ovaries were the main pathological changes observed consistently in almost all diseased ducks. Based on the changes, the disease was diagnosed as duck haemorrhagic ovaritis (DHO), caused by TMUV. Recent studies indicate that TMUV is widely distributed in nature and occurs in a variety of ducks (including Pekin duck, Cherry Valley Pekin duck and Shaoxing duck, Jinyun duck, Longyan duck, Jinding duck and Khaki-Campbell duck). There have been over 10 isolates of TMUV from ducks and chickens reported in the 2 years since the DHO outbreak in the China (Cao et al., 2011; Su et al., 2011; Tang et al., 2012b).

During our investigation of duck TMUV infection, we found the TMUV also caused human infection. This report highlights the emerging nature of this zoonotic disease and calls for attention to its possible public health consequences.

Materials and Methods

Samples collection

A serologic investigation was performed among 132 persons who worked on duck farms or culled birds during the September 2010–October 2012 outbreaks in Shandong, China. Oral swabs were also collected at the same time for virus detection. The samples were screened for the presence of TMUV using semi-nested reverse transcription PCR (SN-RT-PCR) and IgG ELISA. Permission was given before blood, and swab samples were collected from duck cullers and farm workers. The Shandong Agriculture University Research Ethics Committee approved this study.

ELISA method

We detected TMUV-specific antibodies in serum using a ELISA method. In brief, expressed proteins for TMUV E were purified and coated onto the wells (50 ng/well) by incubation at 4°C overnight. The wells were washed three times with phosphate-buffered saline (PBS), pH 7.4 and 0.05% Tween 20 washing buffer. Then, 50 μl of blocking buffer (PBS, 0.05% Tween 20 and 2.5% bovine serum albumin) was added to each well and incubated for 1 h at 37°C to saturate all unbound sites. Coated plates were washed three times with PBS and 0.05% Tween 20. The serum samples diluted at 1 : 100 were added at 100 μl/well and incubated for 1 h at 37°C. After incubation and three washing cycles as described above, 100 μl/well of a 1 : 5000 dilution of horseradish peroxidase (HRP)-labelled goat anti-human IgG was added, and the plates were incubated for 1 h at 37°C and then washed three times with washing buffer. A volume of 100 μl substrate solution containing 0.04% orthophenylenediamine in 0.05 M phosphate-citrate buffer, pH 5.0, and 0.04% H_2O_2 was added. The reaction was carried out for 30 min at room temperature. Colour development was stopped after 10 min by adding 50 μl of 2.5 M H_2SO_4 to each well. The absorbance was read at 450 nm using a plate reader. Duplicate negative control human sera were included in each plate. The ELISA optical density (OD) values for IgG against TMUV higher than 0.689 were considered positive.

Virus neutralization test

We mixed 50% tissue culture infective doses of TMUV strain SDMS (100 U/ml) in 2% foetal bovine serum (Invitrogen, Grand Island, NY, USA) with 2-fold dilutions of heat-inactivated serum samples (1 : 10–1 : 640) in equal volumes and incubated the mixture for 75 min at 37°C in 5% CO_2. Then, the mixture was inoculated onto Vero monolayer cells grown in six-well culture plates (Corning, NY, USA) in 2% foetal calf serum (FCS), 100 U/ml of penicillin and 100 μg/ml of streptomycin. The cell cultures were incubated at 37°C in 5% CO_2 for 72 h. Samples were considered positive for TMUV-neutralizing antibodies if <10% of the cells/well displayed cytopathic effect.

Semi-nested RT-PCR

Oral swab samples from the 132 persons were subjected to RNA extraction (TIANGEN, Beijing, China) for detection of TMUV RNA by NS3-based semi-nested RT-PCR (SN-RT-PCR). In brief, the first round of SN-RT-PCR for the amplification of the NS3 gene was performed with cDNA using 20 pmol of NS3F (5′-ATGGATGAAGCYCATTTCAC-3′) and NS3R (5′- CCAAAGTTGGCYCCCATCTC-3′). The PCR mix containing 5 μl of 10× EX Taq buffer (Mg^{2+} Plus), 1 μl of dNTP mixture (10 mM each dNTP), 5 U EX Taq polymerase (TAKARA, Dalian, China) and 1 μl template cDNA was brought to 50 μl with Rnase-free water. The thermal cycling programme involved an initial denaturation at 94°C for 5 min, followed by 35 cycles, each consisting of denaturation at 94°C for 30 s, annealing at 55°C for 30 s and extension at 72°C for 30 s, with a final extension for 10 min at 72°C. The second round of SN-RT-PCR for the NS5 gene was performed using 1 μl of the first RT-PCR product as the template DNA and 20 pmol/μl of NS3F and SNR (5′-AGCACACGGCAATCTCAT -3′) in the same condition as first round.

Phylogenetic analysis

Phylogenetic analysis was based on nucleotides 277 bases of the NS3 gene. Multiple alignments were constructed using the ClustalW (Ibis Biosciences, Carlsbad, CA, USA) method of the software BioEdit (version 7.0.5.2). The phylogenetic tree was drawn using the neighbour-joining method of the MEGA program (version 4.0) with absolute distances following 1000 bootstrap replicates (Tamura et al., 2007).

Results and Discussion

We have detected TMUV antibodies in serum samples and TMUV RNA in oral swabs from 132 duck industry workers collected during the outbreak of TMUV infection, which suggest human infections with TMUV in China. Our findings demonstrated that the risk for poultry-to-human transmission of the TMUV is high.

In our studies, three diagnostic methods were used for detection of TMUV infection in human. The IgG ELISA gave a positivity rate of 71.9% (95/132 samples), and NS3-based SN-RT-PCR gave the positivity rates of 47.7% (63/132 samples; Table 1).

Table 1. Characteristics for samples from 132 duck industry workers with Tembusu virus infection, Shandong, China

Year	Number of workers	Number of positives		
		IgG ELISA	Virus neutralization	RT-PCR
2010	29	23	15	17
2011	57	38	13	22
2012	46	34	18	24
Control samples[a]	20	0	0	0
Total	152	95	46	63

[a]Samples (serum and oral swab) from 20 non-duck industry workers working as the negative controls in the experiments.

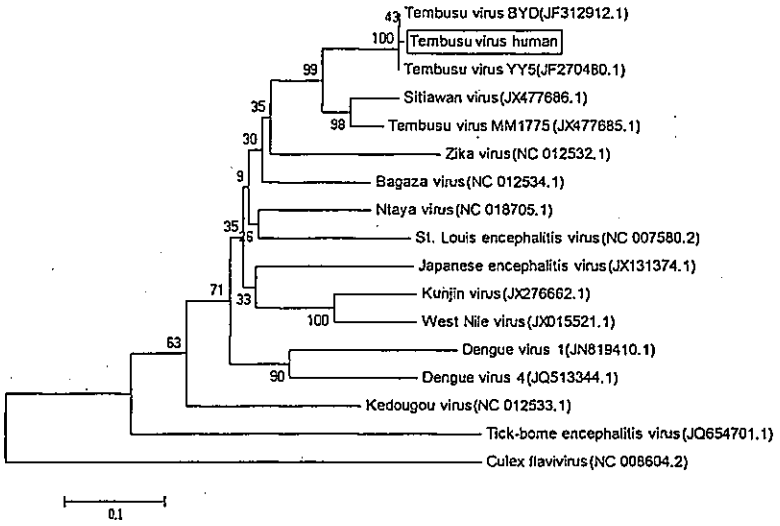

Fig. 1. Neighbour-joining trees based on the NS3 gene of Tembusu virus human strain, China, generated using Molecular Evolutionary Genetics Analysis software (MEGA) version 4.0 (www.megasoftware.net/), the maximum composite-likelihood method and bootstrap analysis of 1000 replicates. TMUV human strain is surrounded by black box. Numbers on branches indicate percentage of replicates that reproduced the topology for each clade. Scale bars indicate estimated evolutionary distance. TMUV, Tembusu virus.

Phylogenetic analysis of TMUV NS3 gene in the oral swab samples from duck farm workers showed a clearly defined grouping into a mosquito-borne flavivirus of the Ntaya virus group, displaying a close relationship with other duck TMUV strains, as reported previously (Fig. 1; Tang et al., 2012a; Yun et al., 2012). BLAST analysis showed that the part of the NS3 gene of human TMUV has almost 100% nucleotide identity with that of BYD virus and YY5 virus, respectively. The NS3 genes of all TMUV strains share about 85.2% and 87.7% nucleotide homology with those of Sitiawan virus and TMUV strain MM1775.

Our studies show evidence of TMUV transmission among groups at high risk for duck-to-human transmission (i.e. exposed to poultry during 2010–2012 outbreaks in Shandong, China), and they suggest a need for increased awareness, enhanced prospective surveillance and a more current serosurvey of TMUV infection in humans. SN-RT-PCR may be a useful diagnostic method during early TMUV infection, but in most TMUV infection cases, serologic tests (e.g. IgG ELISA and virus neutralization) are more likely to yield useful results. For public health reason, further studies should be conducted to isolate human TMUV and investigate its epidemiologic, genetic and pathogenic features.

Acknowledgements

We gratefully acknowledge Tai'an Central Hospital for provided control samples. We also thank Shandong HeKangYuan Farming (Group) Co., Ltd., for provided duck worker samples. This research was supported by the China Agriculture Research System (CARS-43-34), The National Natural Science Funds (31272583) and Shandong Natural Science Funds (ZR2012CM002).

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識別番号・報告回数			報告日	第一報入手日 2013 年 03 月 13 日	新医薬品等の区分 該当なし	厚生労働省処理欄

一般的名称	乾燥濃縮人アンチトロンビンⅢ	研究報告の公表状況	fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/TransmissibleSpongiformEncephalopathiesAdvisoryCommittee/ucm339920.htm/2013/03/12	公表国 アメリカ
販売名 （企業名）	①ノイアート静注用 500 単位　（日本血液製剤機構） ②ノイアート静注用 1500 単位　（日本血液製剤機構）			

研究報告の概要

伝達性海綿状脳症(TSE)諮問委員会第 24 回会合、2013 年 3 月 14 日

話　　題
米国の赤血球製剤輸血に関連する可能性のある変異型クロイツフェルト・ヤコブ病(vCJD)リスクの FDA の定量的リスク評価の予備的結果

要　　約
vCJD は、長期無症候性潜伏期間の致命的なヒトの神経変性疾患である。牛海綿状脳症(BSE)に感染した牛からの牛肉製品への食事暴露は、ヒトの vCJD のありそうな原因である。症候性 vCJD に感染した人は、脳及びリンパ組織中に異常プリオンたん白質が存在する。感染は、血液中にも存在する。赤血球製剤(RBC)輸血による症候性 vCJD3 例と無症候性感染 1 例は、血漿由来第Ⅷ因子製剤による無症候性感染の 1 症例同様に、英国(UK)で報告された。
米国の一部の献血者が英国や特定の他の国への旅行、或いは居住の間に BSE 原因物質に暴露した可能性があるので、それらの人々は無意識のうちに vCJD に感染している可能性がある。輸血感染 vCJD（TTvCJD）のリスクを軽減するために、FDA は英国やヨーロッパの他の国への旅行歴、或いは居住歴のある特定の献血者の献血延期を勧告した。しかし、輸血レシピエントへの若干のリスクは、献血延期方針の限界のために残っている。
FDA は、米国での赤血球製剤輸血を介して感染した vCJD 感染及び臨床疾患の確率を推定するためのリスク評価を実施した。そのリスク評価モデルの開発において、FDA は英国での vCJD の想定有病率の 2 つの異なる値を使用した。高有病率の入力は英国からの匿名の扁桃腺及び虫垂検体で検出された異常プリオン蛋白質の反応データから派生したもので、低有病率の入力は英国での vCJD のモデリングに基づいていた。リスク評価のために用いた FDA モデルで得られた結果は、この特定の有病率の入力に大きく依存している。1 赤血球製剤単位の輸血による予測リスクは、高有病率の入力を用いた場合、1/48 万（2.5～97.5 ﾊﾟｰｾﾝﾀﾙ：1/4.3 百万～1/110,574）であり、低有病率の入力を用いた場合、1/134 百万（2.5～97.5 ﾊﾟｰｾﾝﾀﾙ：0～1/8.7 百万）である。
症候性 vCJD 感染（米国で報告された vCJD 症例数、英国とフランスの TTvCJD 症例）の現在の疫学に対する英国の高低一推定有病率を用いたそれぞれのモデル入力の比較に基づき、そして英国の虫垂データの重要性に関する現在の科学的な不確実性を考慮して、FDA は米国での TTvCJD のリスクを代表するものとして、英国の高い想定有病率に基づくモデル出力よりも、英国の低い想定有病率に基づくモデル出力の方が、より類似していると信じている。
FDA はデータ入力、モデル構造、仮定及び結果が妥当であるかどうか、そして米国での TTvCJD のリスクが、非常に小さいと考えられる FDA の暫定的な解釈の賛否について、委員会の助言を求めている。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1)略
1)略
2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

文献番号 11

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報告企業の意見	今後の対応	
血漿分画製剤は理論的な vCJD 伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を 2003 年 5 月から添付文書に記載している。2009 年 2 月 17 日、英国健康保護庁(HPA)は vCJD に感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD 異常プリオン蛋白が検出されたと発表したが、日本血液製剤機構の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内での BSE の発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは 1999 年以前の英国に比べて極めて低いと考える。また、本剤の製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。	

Transmissible Spongiform Encephalopathies Advisory Committee
24th Meeting, March 14, 2013

Topic

Preliminary results from FDA's quantitative risk assessment of the vCJD risks potentially associated with the transfusion of red blood cells in the U.S.

Issue

FDA seeks advice from the Committee on the inputs, model structure and interpretation of its draft Risk Assessment for the risk of vCJD from red blood cells in the US.

Summary

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal human neurodegenerative disease with a long asymptomatic incubation period. Dietary exposure to beef products from cattle infected with bovine spongiform encephalopathy (BSE) is the likely cause of human vCJD. Individuals with symptomatic vCJD infection have abnormal prion protein present in brain and lymphoid tissue. Infectivity is also present in blood. A total of three symptomatic vCJD infections and one asymptomatic infection transmitted by red blood cell (RBC) transfusion, as well as one case of asymptomatic infection linked to use of plasma-derived Factor VIII, have been reported in the United Kingdom (U.K.) (Llewelyn et al., 2004; Peden et al., 2010; Peden et al., 2004; HPA, 2006; HPA, 2007).

Since some U.S. blood donors may have been exposed to the BSE agent during travel or residence in the U.K. or certain other countries, these individuals may have unknowingly been infected with vCJD. In order to reduce the risk of transfusion-transmitted vCJD (TTvCJD), FDA has recommended deferral of certain blood donors with a history of travel to or residence in the U.K. and other countries in Europe (FDA, 2010a). However, some risk to transfusion recipients remains because of the limitations of deferral policies.

FDA conducted a risk assessment to estimate the probability of vCJD infection and clinical disease acquired through RBC transfusion in the U.S. In developing its risk assessment model, FDA used two different values for the assumed prevalence of vCJD in the U.K. A high prevalence input was derived from data on abnormal prion protein reactivity detected in anonymous tonsil and appendix samples from the U.K., and a low prevalence input was based on modeling of vCJD in the U.K. Results obtained with the FDA model used for risk assessment are highly dependent on this particular prevalence input. The predicted risk with transfusion of one RBC unit using the high prevalence input is 1 infected unit in 480,000 units transfused (2.5 to 97.5 percentile: 1 in 4.3 million to 1 in 110,574) and using the low prevalence input is 1 in 134 million (2.5 to 97.5 percentile: 0 to 1 in 8.7 million).

Based upon a comparison of the respective model outputs using the high and the low UK prevalence estimates against the current epidemiology of symptomatic vCJD infection (number of reported vCJD cases in the US, and TTvCJD cases in the UK and France), and taking into consideration current scientific uncertainty regarding the significance of the U.K. appendix data,

FDA believes that the model output based on the low UK prevalence assumption is more likely than that based on the high UK prevalence assumption to represent the risk of TTvCJD in the U.S.

FDA seeks the advice of the committee on whether or not the data inputs, model structure, assumptions, and results are reasonable, and whether they agree with FDA's interim interpretation that the risk of TTvCJD in the U.S. is likely to be very small.

Background

Dietary exposure to beef products from BSE-infected cattle is the likely cause of primary vCJD (Bruce et al., 1997; Hill et al., 1997). vCJD is a fatal human neurodegenerative disease with a long asymptomatic incubation time. Individuals with symptomatic vCJD infection have abnormally folded prion protein (PrPTSE) present in brain and lymphoid tissue. Infectivity is also present in blood, given that several cases of TTvCJD have been observed in the U.K. Therefore, a blood donor, unknowingly infected with vCJD and healthy at the time of donation, could potentially donate infectious blood. As of December 2012, a total of 227 vCJD cases have been recognized worldwide, of which 176 cases were reported from the U.K. and 27 cases from France (two French vCJD cases are currently alive). The risk that donors of RBC in the U.S. may acquire vCJD infection through consumption of U.S. beef is thought to be negligible, because BSE has been detected in so few U.S. cattle. In particular, there have been only four reported U.S. cases of BSE: three in U.S.-born cattle and one in a cow imported from Canada (CDC, 2012; USDA, 2013). In addition, none of the three cases of vCJD recognized in individuals in the U.S. appears likely to have resulted from U.S. exposure: two cases occurred in long-time U.K. residents and a third occurred in a recent immigrant from Saudi Arabia. However, some U.S. blood donors might have been exposed to the BSE agent during travel or residence in the U.K. and other countries with increased BSE risk.

In 1999, consistent with advice from the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC), FDA recommended precautionary deferral of blood and plasma donors who had traveled or lived for six months or longer in the U.K. during the period from the presumed start of the BSE outbreak in 1980 until the end of 1996, when the U.K. had fully implemented a full range of measures to protect animal feed and human food from contamination with the BSE agent (TSEAC, 1999). In 2002, FDA recommended enhancing the vCJD geographical donor deferral policy by reducing the time that an otherwise suitable blood donor might have spent in the U.K. from six to three months (FDA, 2002). FDA also recommended deferring donors who had spent five or more years cumulatively in France or other countries in Europe listed by the USDA as either having had BSE or having had a significant risk of BSE, and donors with a history of blood transfusion in the U.K. after 1979. In 2010, FDA issued a revised guidance document to include deferral of blood donors transfused in France since 1980 (FDA, 2010a).

No cases of TTvCJD have been identified in the U.S. However, some risk to the recipients of blood and blood products may exist. From 2003 to 2010, FDA conducted risk assessments for potential risk of vCJD transmitted via U.S.-licensed plasma-derived products, factor VIII

(pdFVIII) to patients with severe hemophilia A or von Willebrand disease (type-3 vWD) and via U.K.-manufactured factor XI to a small group of U.S. patients who participated in an investigational drug study. The risk assessment and their revisions were presented at TSEAC meetings in 2006, 2009 and 2010. Based on the results of these risk assessments, FDA concluded that "the risk of vCJD transmitted via plasma-derived products is highly uncertain, but likely to be extremely small" (FDA, 2006a; FDA, 2006b; FDA, 2010b). The considerations for the assessment of vCJD risk for plasma-derived products vary somewhat from those for RBCs. During manufacturing, plasma from thousands of donors is pooled for processing, and a unit of plasma from a single infected donor has the potential to contaminate a large batch of product that may be transfused into hundreds of patients. However, plasma fractionation and other purification steps significantly reduce risk by removing most of the infectious vCJD agent from the final purified product. By contrast, the risk from an RBC unit is different because it is not processed and is collected from a single donor and most often administered to a single recipient. Thus, the TTvCJD risk for an RBC unit is likely to be higher for a single recipient than that for a person treated with a plasma derivative.

Cases of TTvCJD have been documented in the U.K. during the past ten years. A total of three symptomatic vCJD infections (HPA, 2006; HPA, 2007; Llewelyn et al. 2004) and one asymptomatic infection transmitted by RBC transfusion (Peden et al., 2004), as well as one case of asymptomatic infection linked to use of plasma-derived Factor VIII, have been reported (Peden et al., 2010). In addition to these epidemiologic data, there are also informative data on the number of individuals potentially exposed to vCJD derived from the immunohistochemical examination of thousands of archived surgical specimens. In particular, studies have examined lymphoid tissues, including tonsil and appendix, since they are known to have detectable abnormal prion protein (PrP^{TSE}) in symptomatic individuals dying with vCJD. An initial study including 12,674 evaluable appendectomy and tonsillectomy specimens from the U.K. found accumulations of the abnormal prion protein in three appendectomy specimens, providing an estimate of 237 vCJD infections per million population (95% CI 49-692 per million persons) (Hilton et al., 2004). A further study in 63,007 anonymous tonsil specimens from the U.K. found no abnormal prion protein when screened by a relatively insensitive immunoassay (Clewley et al., 2009), but reevaluation of a subset of the same tonsil specimens with a more sensitive immunohistochemical technique yielded an inconclusive positive result (de Marco et al., 2010). A second appendix survey using immunohistochemistry detected abnormal PrP in 16 of 32,441 U.K. samples, leading to a final mean estimate of 493 possible latent vCJD infections per million persons (95% CI: 282-801 per million persons) in the U.K. (HPA, 2012).

The significance of the findings from the tonsil and appendix studies is not fully known. The appendectomy findings may have identified a group of individuals who will eventually develop symptomatic vCJD after a time to onset dependent, at least in part, on the *PRNP* codon-129 genotype. Almost all individuals symptomatic with vCJD to date have been methionine-homozygous (MM) at *PRNP* codon 129. However, one individual of the MV genotype was diagnosed with vCJD, though tissue never became available to confirm the diagnosis by testing for PrP^{TSE} (Kaski et al., 2009). It is believed that at least some infected non-MM genotypes will eventually develop vCJD later. Since the appendix survey potentially reflects the highest prevalence of latent infection in the U.K. population demonstrated to date, data from this study was used in the model presented subsequently as the "high-prevalence" estimate.

Because the data from the appendix survey were de-identified, it is difficult to learn whether any individuals with abnormal prion protein detected in the appendix later developed symptomatic disease; preliminary current analysis suggested that none have so far (HPA, 2012). To date, efforts to transmit vCJD agent from the reactive appendices to experimental animals have not been informative. In addition, considering the apparent discordant results of the tonsil and appendix surveys, and given the epidemiology of overt cases of vCJD in the U.K. to date, it is possible that the finding of PrP^{TSE} in appendices represents cross-reactivity with another protein, rather than detecting the misfolded PrP generally associated with the infectious TSE agent in tissue. Finally, even if appendiceal involvement truly indicates vCJD infection, the time that must elapse for infectivity to appear and circulate in blood is unknown. In short, it remains unknown whether the findings of the U.K. appendix survey reliably indicate the true prevalence of latent vCJD infections in the U.K. population, and if so, how many persons with latent vCJD infection will ultimately develop overt disease, or whether the blood of some latently infected persons contains the transmissible agent. U.K. authorities have offered precautionary responses to each of those questions (HPA, 2012).

FDA Risk Assessment for Transmission of vCJD via RBC Transfusion

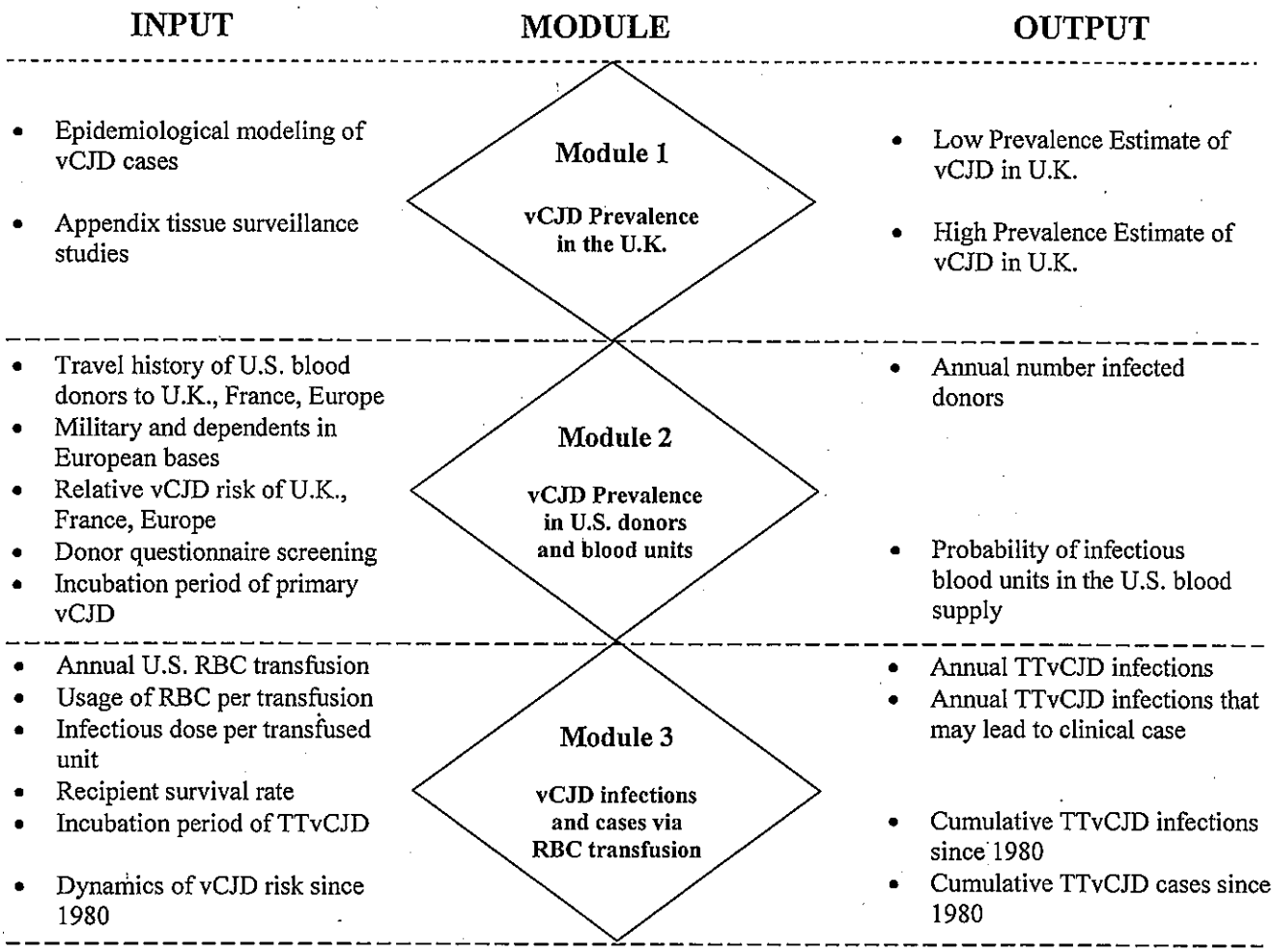
FDA conducted a risk assessment to explore the potential risk of vCJD transmission through RBC transfusion. The RBC risk assessment model estimated the annual risk of TTvCJD infections for the year 2011 and the number of infections that may progress to clinical cases in the future. The risk assessment model also estimated cumulative numbers of infections and clinical cases for the years 1980 through 2011 resulting from RBC transfusion. To better understand whether the model used generated reasonable estimates of vCJD infections and cases, FDA compared the results from the model to the number of observed vCJD cases in the U.S. and the observed TTvCJD cases in the U.K. and France.

I. Overview of the FDA Risk Assessment Model

The FDA developed a computer-based simulation model consisting of three modules (Figure 1). The U.K. vCJD prevalence is estimated in Module 1; U.K. prevalence provides the foundation of the model used to generate other critical prevalence estimates. The estimated prevalence is applied in Module 2 to generate estimates of vCJD prevalence for France, for other countries in Europe and for U.S. military personnel posted to bases in Europe. vCJD risk is then estimated for U.S. blood donors who have traveled to these countries since 1980. The risk for a U.S. blood donor is calculated as a proportion composed of travel time spent in the destination country (where the donor may have been exposed to the BSE agent) versus risk for a permanent resident who is assumed to have lived in the destination country for all 16 years of the whole risk period (at which point the resident's risk is equivalent to the country's vCJD prevalence). FDA assumed the risk period in the U.K. began in 1980, when the epidemic of BSE is thought to have started in the U.K., and to end in 1996 when strict risk control measurements were rigorously implemented in the U.K. The use of 16 years as the exposure interval for other countries in Europe represents a simplified approximation, reflecting the belief that the predominant portion of the risk in these countries had been reduced since 1996 because of the ban on U.K. beef exports and the reduced

risk from U.K. beef itself. This proportion is then multiplied by the vCJD prevalence for the country or region to obtain the vCJD prevalence for the U.S. donor. Accordingly, the model incorporates estimates of vCJD prevalence for the destination country; donor travel data such as destination, year and duration; and the efficiency of U.S. donor deferral policies in removing infected donors to generate the probability of vCJD infection of a U.S. blood donor(s). In Module 3, one model output estimates the number of possible TTvCJD infections among U.S. RBC transfusion recipients for the year 2011 based on the total annual number of blood donations and transfusions, amount of blood used per transfusion and the quantity of infectious agent per unit of blood; a second output provides estimates the number of TTvCJD infections that may progress to clinical cases (accounting for the incubation period of the disease and post-transfusion survival of the RBC recipients). Finally, the number of infections for the year 2011 is extrapolated for the number of infections for the individual year between 1980 and 2011 and then summed to generate a cumulative estimate of the number of TTvCJD infections and cases.

Figure 1. Exposure Assessment Model Diagram



Most model inputs (assumptions) are statistical distributions representing the variability and uncertainty associated with the input variables. These are shown in Table A-1 of the Appendix. Many of the input distributions or values used in this risk assessment are the same as those used in the previous FDA pdFVIII Risk Assessment (FDA, 2010b). However, some inputs have been updated based on new scientific research data and information (Table 1). Monte Carlo simulation was applied to integrate variability and uncertainty of all model inputs by randomly selecting a single input value from a statistical distribution of each input variable, applying the appropriate mathematical functions to generate a result for each iteration or run of the model. The model was run tens of thousands of times and the results/output was assembled in a final aggregate distribution. The outputs of the distributions are described using the mean and the 2.5th and 97.5th percentiles.

Table 1. Summary Update of Input Assumptions for Current FDA RBC Risk Assessment (2013) from Previous FDA FVIII-vCJD Risk Assessment (2010)

Input Name	Current FDA RBC Risk Assessment (2013)	Previous FDA FVIII Risk Assessment (2010)	Justification
U.K. vCJD Low Prevalence Estimate	1.7 per million* (0.2-3.7 per million)	~4.5 per million	Current Low Prevalence Estimate used in the FDA RBC Risk Assessment (2013) used updated epidemiological model by Garske and Ghani (Garske and Ghani, 2010). Previous FDA FVIII Risk Assessment model (2010) Low Prevalence Estimate was generated using epidemiological model by Clarke and Ghani (Clarke and Ghani, 2005).
U.K. vCJD High Prevalence Estimate	493 per million* (282 - 801 per million)	267 per million * (55 - 779 per million)	Current High Prevalence Estimate used in the FDA RBC Risk Assessment (2013) was updated to include new results from surveys with a much larger number of appendices (HPA, 2012b). Previous High Prevalence Estimate for the FVIII Risk Assessment model (2010) was generated based on the first appendix study (Hilton et al., 2004).
Relative risk for France	10% (of UK)	5% (of UK)	Current relative risk for France in the FDA RBC Risk Assessment (2013) was updated to reflect the increased rate of cases in France relative to the UK. Accordingly, we increased the Relative Risk of France to 10% in this Red Cell Risk Assessment. Previous FDA FVIII risk assessment (FDA, 2010b) we assumed the Relative Risk for France is 5% of the UK risk.
Risk for France	1980 - 2001	1980 - current	Current risk for France in the FDA RBC Risk Assessment (2013) was updated to account for additional BSE and human food safety control measures implemented in France since 2001 (Afssa, 2007). Accordingly, we reduced the number of years in the risk window period for France to include the years 1980 through 2001. Previous FDA FVIII Risk Assessment (FDA, 2010b) assumed a risk period for France ranging from 1980 to present.
Incubation period for primary vCJD in MM	Lognorm distribution: Mean=15 years,	Gamma distribution: Mean=15 years,	Current incubation period for primary vCJD in MM persons in the FDA RBC Risk Assessment (2013) was updated and the 5th percentile value was changed based on CDC's assumption that the minimum incubation

	Median=12 years 5th =9 years, 95th =35 years	Median=12 years 5th=5 years, 95th=35 years	period for vCJD in MM is 9 years. No Gamma distribution fit the required mean, medium, 5th and 95th, therefore, the Gamma distribution was replaced by Lognorm distribution.
Incubation period for primary vCJD in non-MM	Lognorm distribution: Mean=35 years, Median=32 years 5th =23 years, 95th =55 years	Gamma distribution: Mean=35 years, Median=32 years 5th=25 years, 95th=55 years	Current incubation period for primary vCJD in non-MM persons in the FDA RBC Risk Assessment (2013) was updated and the 5th percentile value of 23 years was calculated by summing 9 years (5th for MM) plus 14 years (the time delay on the appearance of the first MV case from that of the first MM case). No Gamma distribution fit the required mean, medium, 5th and 95th, therefore, the Gamma distribution was replaced by Lognorm distribution.
Infection dose in blood of infected donors	**ID per transfused unit** (1 transfused unit=500 ml) Triangular distribution (min, most likely, max) of 0.56, 0.75, 0.96	**ID_{50} per ml blood** Lognorm distribution Min=0.1 5th perc =2 median=12 95th perc =30 Max=1000	We recently reported a statistical analysis of published data from sheep transfusion experiments and U.K. Transfusion Medicine Epidemiology Review suggesting that the infection dose in infected blood is likely to be lower than previously assumed (Gregori et al., 2011). In our FVIII risk assessment we assumed a higher probable dose of infectious agent in blood of humans incubating vCJD based on published rodent studies.
Donor age	10-year age shifting to reflect aging of the donor populations	Age reported in a U.S. blood donor travel survey conducted in the year 2000	Donor travel data used in FDA model was collected approximately 10 years ago. In Red Cell Risk Assessment donor age was shifted by 10 years to reflect current donor age in 2011. In previous FVIII Risk assessment model we used donor age reported in the donor travel survey.

*mean value with 95% confidence interval in parentheses

Module 1- vCJD Prevalence in the U.K.

This module estimated vCJD prevalence in the U.K., which in turn was used as the basis for estimating vCJD prevalences in France and other countries in Europe. These prevalence values were then used to estimate the risk of vCJD infection in U.S. blood donors who traveled to the U.K., France and other countries in Europe as a proportion based on the time spent in the country versus a permanent resident who lived for the entire 16 years of the simplified risks period (using risk period for the U.K. 1980-1996 as reference). Because of the considerable uncertainties associated with estimating vCJD prevalence, we derived two estimates of U.K. vCJD prevalence using two different data sources. The FDA computer model calculated risk outcomes stratified by these two prevalence estimates. The discrepancy between these two prevalence estimates contributed the greatest amount of uncertainty to the final risk estimates – more uncertainty than for any other parameters used in the model.

Low Prevalence Estimate:

Epidemiological modeling by a U.K. research group (Garske and Ghani, 2010) predicted 100 (95% CI: 11-220) primary cases remaining after 2010. Since 1996 the U.K. has implemented a full range of measures to protect animal feed and human food from contamination with the BSE infectious agent. Accordingly, FDA assumed no primary vCJD infections were acquired in the U.K. after 1996, and all predicted cases after 2010 were incubating in 2011. Given a total U.K. population of about 60 million, the estimated number of future vCJD cases was translated to a

mean prevalence of approximately 1.7 asymptomatic vCJD infections per million U.K. population (95% CI: 0.2-3.7 infections per million) in year 2011.

High Prevalence Estimate:
This estimate is based on the detection of accumulated abnormal prion protein (PrP^{TSE}) in tissues of the lymphoreticular system. After an initial finding of three PrP^{TSE} positive appendices out of 12,674 stored tonsil and appendix tissues from U.K. patients in 2004 (Hilton et al., 2004), a subsequent study tested 32,441 archived appendix specimens and found 16 positive specimens (HPA, 2012). The prevalence with a mean estimate of 493 infections per million persons (95% CI: 282-801 per million persons) calculated based on the second study was recently endorsed by the U.K. Advisory Committee on Dangerous Pathogens TSE Risk Assessment Subgroup (ACDP 2012).

Module 2- vCJD Prevalence in U.S. Blood Donors and Blood Units

This module estimates the annual number of U.S. blood donors who were at risk of vCJD infection because of travel to the U.K., France and other countries of Europe, who may have been exposed to the BSE agent, infected with vCJD and carried vCJD infectious agent in their blood at the time of donation. The outcome of the module provides the probability of an infectious blood unit entering the U.S. blood supply for transfusion.

First, the module calculated the annual number of U.S. blood donors who were at risk of vCJD infection due to travel to or residence in the U.K., France and other countries of Europe using data from a blood donor travel survey (TSEAC, 2000). The survey was conducted by American Red Cross (ARC) in the year 2000, collecting information on blood donors and their history of travel to the U.K., France and other countries of Europe during a risk period between 1980 and 1996 (TSEAC, 2000). FDA modeled risk for four groups of U.S. donors: (1) donors who traveled to or lived in the U.K. during the years 1980-1996, (2) donors who traveled to or lived in France during the years 1980-2001, (3) donors who traveled to or lived in other countries in Europe since 1980, and (4) donors deployed to a U.S. military base in Europe during the years 1980-1996.

Second, the module calculated the risk of vCJD infection of U.S. donors based on their age, destination, year and duration of travel. The module integrated estimates of UK vCJD prevalence (from Module 1) and the relative risk for France, other countries in Europe, and U.S. military personnel posted to bases in Europe (relative risk for UK, France, other countries in Europe and military bases are 1, 0.1, 0.015 and 0.35, respectively) to derive the vCJD prevalence for the different at-risk countries. Relative risk of specific at-risk countries was determined based on factors such as the number of reported vCJD cases in humans, the amount of beef imported from the U.K., the number of domestically acquired case of BSE in cattle, and other factors (TSEAC, 1999). The model allocated risk to each individual year in the 16-year risk period (1980- 1996) for the U.K. by assuming that the risk of exposure in a specific year was in proportion to the number of BSE cases reported in that year. The model further assumed that the risk of exposure was in proportion to the duration of stay in the at-risk countries, and that donors who had

cumulative stays of 5 years or longer in an at-risk country during the years between 1980 to 1996 had the same risk as a full-time residents of that country.

Third, the module calculated the total number of infected donors, the number of donors whose blood contained infectious vCJD agent at the time of donation and the probability that a blood unit might have contained the infectious agent in 2011. The FDA model assumed vCJD agent most likely first appears in the blood of infected persons during the last 75% of the incubation period (that is, after 25% of the incubation period has elapsed). The infectivity might first appear, at the earliest, during the last 90% of the incubation period (that is, after 10% of the incubation period has elapsed) and at the latest after 50% of the incubation period has passed. Therefore, only a portion of infected donors may actually have infectious agent in their blood at the time of donation. The model also incorporated the risk reduction effect of FDA's recommended donor deferral policies. The FDA model assumed the efficiency of the donor questionnaire to identify at-risk donors (and remove them from the donor pool) to range from 85% to 99%. The vCJD donors who actually donate were either not deferred by current FDA recommendation because of limitations in the screening such as short-term travel that falls below FDA guidelines or failure to recall travel, among other explanations.

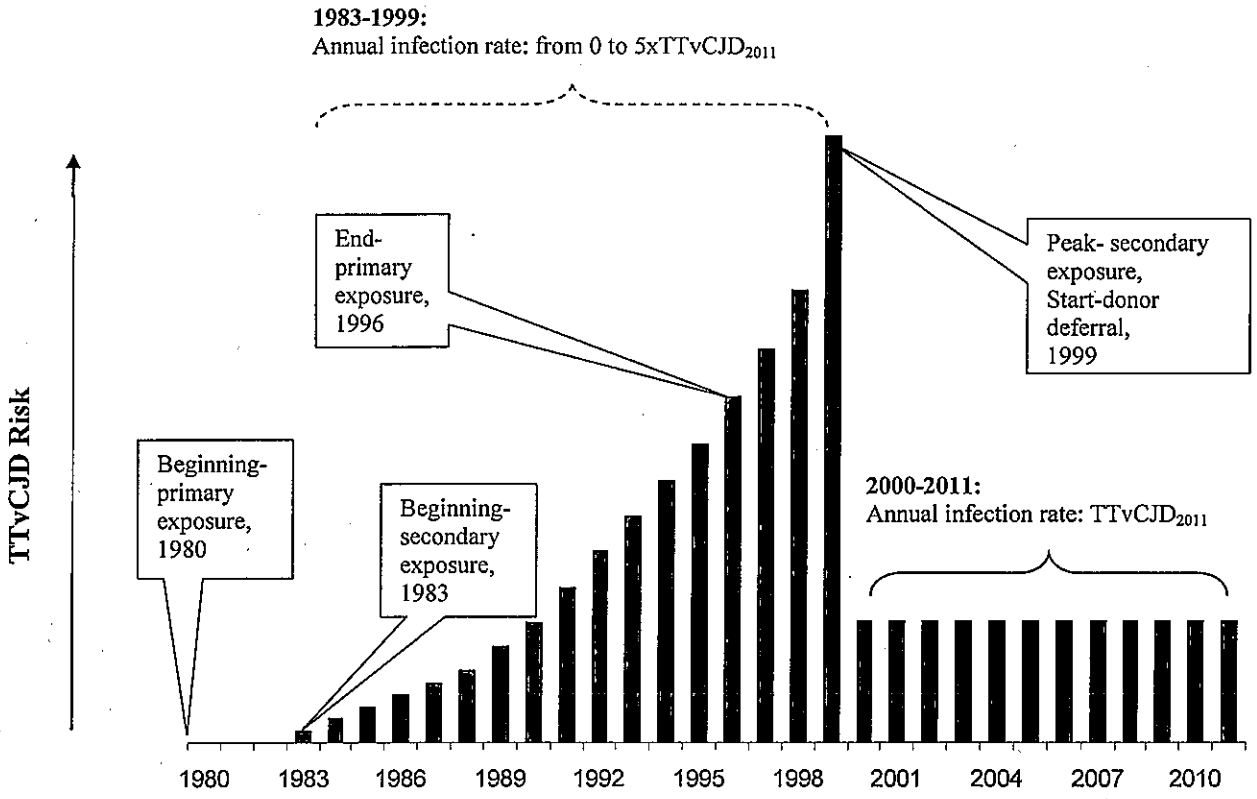
Module 3- vCJD Infections and Cases in the U.S. via Blood Transfusion

Incorporating data and information on U.S. blood donation and transfusion (Anderson et al., 2007; HHS, 2009), this module calculated the probability a U.S. RBC recipient would receive a RBC unit containing an infectious dose based upon the estimated vCJD prevalence in the U.S. blood supply (calculated in Module 2). As explained in a published analysis of data from the U.K. Transfusion Medicine Epidemiological Review (TMER, 2013), FDA assumed that a unit of infectious RBC would likely contain a mean of 0.75 infectious doses (ID) with a range of between 0.56 and 0.96 ID (Gregori et al., 2011). The module calculated the annual number of TTvCJD infections acquired in the year 2011 and further calculated the number of these infections that may progress to clinical cases after adjustment for post-transfusion survival. Extrapolating from the incubation time for the development of vCJD following consumption of BSE-contaminated beef, FDA assumed the incubation period for TTvCJD in persons of the MM genotype as a mean of 10 years with a range of 6-20 years, the incubation period for TTvCJD in persons of the non-MM genotype being a mean of 20 years with a range of 16-30 years. Infection was assumed to progress to an overt clinical case of vCJD only when patient's survival exceeds the incubation period.

The module also calculates the cumulative number of TTvCJD infections acquired since 1980 and the cumulative number of TTvCJD clinical cases that should have been observed (Figure 2). FDA assumed there was a three-year delay in the appearance of infectious agent in the blood of an infected person from the time of infection (since it is assumed that infectious agent does not appear in blood until 25% of the 12-year median incubation period has elapsed). TTvCJD risk emerged in the U.S. in year 1983 (three-year delay from beginning of risk of BSE exposure in 1980), peaked in 1999 (three-year delay from 1996, the end of risk period for food-borne vCJD in the U.K.), was reduced by approximately five-fold (as indicated by model result) after 1999 because of implementation of current donor deferral policy (80% risk-reduction provided by donor deferral), and then remained unchanged after 2000. The total cumulative number of

clinically overt TTvCJD cases expected to have been observed during the years 1980 through 2011 was calculated (taking into account the incubation period of TTvCJD and post-transfusion survival rate).

Figure 2 Graphic Representation of Calculations Used to Estimate Cumulative Risk for TTvCJD in the U.S. During the Years 1980 Through 2011



II. Model Outputs for U.S. Risk of TTvCJD

The FDA RBC risk assessment estimates the potential number of vCJD infections acquired through RBC transfusions in the U.S. during the year 2011, and the number of those infections that progress to clinical cases. The risk assessment also estimates the total number of cumulative vCJD infections predicted to occur between 1980 and 2011 and the number of clinical cases predicted to occur by 2011. The mean, 2.5th and 97.5th percentile values shown in Table 2 briefly summarize of the aggregate output distributions generated by the model.

Table 2. Model Results Showing the Mean vCJD Infection Risk per RBC Transfusion, the Mean TTvCJD Risk for the Year 2011 and the Total Mean Cumulative Risk for the Years 1980 Through 2011 in the U.S. (2.5^{th}-97.5^{th} percentiles shown in parentheses).

		Annual risk (2011)		Cumulative risk 1980-2011	
	Risk per RBC transfusion	Infections	Clinical cases	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)*	0.8 (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)	210 (0-942)	9 (0-47)

*The (2.5^{th}-97.5^{th}) values of (0,0) indicate that the predicted risk is zero or nearly zero. Specifically, for at least 97.5% of the model runs there are zero infections or clinical cases predicted.

Using the low vCJD prevalence assumption, the model estimated that the chance of receiving an infected unit in a transfusion is a mean of 1 in 134 million. The estimate with the high vCJD prevalence assumption resulted in a mean of 1 in 480,000. The model also estimated an annual risk of zero TTvCJD infections for the year 2011 with the low prevalence scenario and six TTvCJD infections with the high prevalence scenario. The TTvCJD infections acquired in 2011 would lead to 0 and 1 clinical case for low and high prevalence estimates, respectively. The model also estimated a mean of approximately one cumulative infection and zero clinical cases when the low prevalence estimate was used, and a mean of 210 infections and 9 possible clinical cases when the high prevalence estimate was used.

III. Model Validation: Model Predictions versus Observed cases

1. Primary vCJD cases in the U.S.

To better understand whether the model used generated reasonable estimates of vCJD infections and cases, we compared the results from the model to the number of observed vCJD cases in the U.S. For this model validation, we extrapolated model results for the number of vCJD cases predicted for the U.S. blood donors and adjusted the number to reflect the larger general U.S. population. We then predicted the total cumulative primary vCJD cases in the U.S. population since 1980 to compare with number of cases actually observed. Three vCJD cases have been reported in the U.S. since 1980. Based on their history of residence, CDC attributed all three cases to infection acquired outside the U.S. (CDC, 2010). The model predicted cumulatively a mean of one case of vCJD in the U.S. since 1980 when the low prevalence estimate was used and 256 cases when the high prevalence estimate (Table 3) was used. The model predictions derived

using the low prevalence estimate was generally consistent with the three vCJD cases actually reported in the U.S. to date; using the high prevalence estimate, the model predicted many more overt clinical cases than have actually been observed.

Table 3. Observed and model-Predicted Mean Numbers of vCJD Cases in the U.S. (2.5^{th}-97.5^{th} percentiles shown in parentheses)

Observed cases*	Model Prediction (cases)	
	Low Prevalence Estimate (1.7 infections per million)	**High Prevalence Estimate** (493 infections per million)
3	1 (0-8)	256 (0-528)

*Note that CDC attributed all three cases to infection acquired outside of the U.S.

2. TTvCJD Cases in the U.K. and France

We further used the model to predict the numbers of cumulative TTvCJD cases in the U.K. and France for the years spanning 1980 through 2011 and compared the model predictions with observed numbers of TTvCJD cases reported in these two countries. Three clinical vCJD cases associated with blood transfusion have been identified in the U.K., and zero cases have been reported in France. For the years 1980 through 2011 the model predicted means of one and 289 cumulative TTvCJD cases for the U.K.; and zero and 33 cases for France using the low and high prevalence estimates, respectively (Table 4). Using the low U.K. prevalence estimate, the FDA model predicts numbers of cases of TTvCJD in the U.K. and France that are generally consistent with reported numbers of cases; the high U.K. prevalence estimate causes the model to overestimate greatly the number of clinical cases of overt vCJD attributed to transfusion to date.

Table 4. Observed and model-Predicted Mean Numbers of TTvCJD Cases in the U.K. and France (2.5^{th}-97.5^{th} percentiles shown in parentheses)

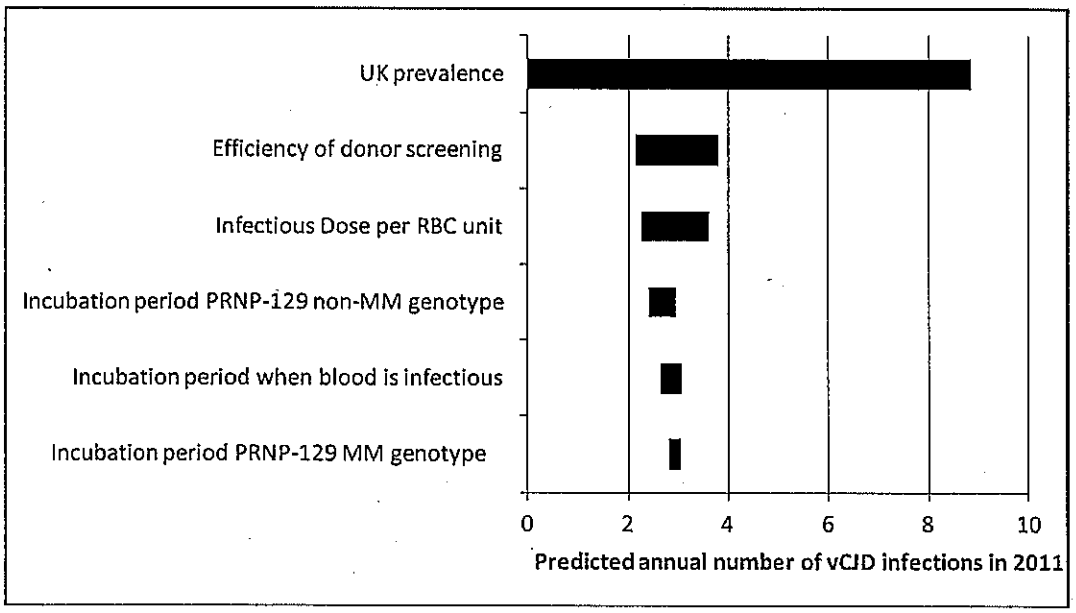
	Observed cases	Model Predictions (cases)	
		Low Prevalence Estimate (1.7 infections per million)	**High Prevalence Estimate** (493 infections per million)
U.K.	3	1 (0-7)	289 (3-925)
France	0	0.2 (0-0)*	33 (0-0)*

*The (2.5^{th}-97.5^{th}) values of (0,0) indicate that the predicted risk is zero or nearly zero. Specifically, for at least 97.5% of the model runs there are zero infections or clinical cases predicted

IV. Importance/sensitivity Analysis

An importance analysis was conducted to determine which inputs in the FDA RBC risk assessment model would have the largest impact on the model estimates of risk. The output variable selected for the importance analysis was the annual number of infections in the U.S. during the year 2011. Six input variables selected were the following: the U.K. vCJD Prevalence, Efficiency of Donor Screening, Infectious Dose (ID) in a unit of RBCs, Incubation Period Primary vCJD PRNP-129 MM genotype, Incubation Period when Blood is Infectious, and Incubation Period Primary vCJD PRNP-129 non-MM genotype. The statistical distributions of these model inputs were generated using assumptions based on limited data and information for human vCJD, published findings for other TSEs or other animal models; accordingly, they are less certain than the other model inputs. The importance analysis was conducted using Monte Carlo simulation sequentially varying each of the inputs from a low value to a high value while randomly selecting values of other inputs from statistical distributions. The low and high values of the inputs were the 2.5^{th} and 97.5^{th} percentile of input distributions used in FDA RBC risk assessment (see Table A-1 in the appendix). The variation between the results obtained for the low and high values were aggregated by input variable and plotted as a tornado chart (Figure 3). The results of the importance analysis indicated that the model input for the U.K. vCJD prevalence estimate had the greatest impact on the model estimation of the annual number of vCJD infections in the U.S. in year 2011. The risk driver of next greatest impact is the efficiency of donor screening.

Figure 3. Importance Analysis: Impact of Input Variables on the Model Outputs for the Annual Number of Infections in U.S. Donors in 2011



V. Uncertainties and Data Gaps

The largest uncertainty in this RBC risk assessment is associated with the estimates of U.K. vCJD prevalence. There is a large discrepancy between the low and high prevalence estimates used in the model, and both prevalence estimates have their limitations. The low prevalence estimate was calculated based on estimates of the future number of vCJD cases in the U.K. as predicted by an epidemiological model (Garske and Ghani, 2010) under many simplifying assumptions. Although these simplifying assumptions are a necessary part of vCJD case estimation efforts, they contribute considerable uncertainty to the final number of cases estimated by the model. Since the low prevalence estimate was derived based on modeling of vCJD cases, it is perhaps not surprising that it more accurately "predicted" the number of overt clinical cases observed. The high prevalence estimate, calculated using data from the appendix tissue surveillance study (HPA, 2012), also has its limitations. Among others, one major limitation is that neither the sensitivity nor specificity of the immunohistochemical tissue testing method used to identify persons who might be infected with the vCJD agent has been well established. In order to reduce the uncertainties for the very different U.K. vCJD prevalence estimates used in our model, more studies are needed to understand variations in infection and eventual progression of infections to cause overt vCJD. Many questions remain unanswered. These include the features associated with susceptibility of the human population and subpopulations to vCJD infection and disease, duration of the incubation period, and the dependency of susceptibility and incubation period on the age and genotype of persons exposed to the agent. This information is critical to reconcile prevalence estimates from the epidemiological model and tissue studies and for determining which of the two prevalence estimates more accurately reflect TTvCJD risk and should be used in risk assessment to support risk management decisions.

VI. Discussion

At first glance, the FDA risk assessment and the recently revised analysis by the UK Department of Health's Health Protection Analytical Team (HPA, 2013) might seem to have yielded quite different estimates for the future likelihood of transfusion-transmitted vCJD in the UK and US. The apparent differences largely result from different approaches we took to deal with the apparent inconsistency between (1) a high prevalence of latent vCJD infections in the UK implied by results of the PrP^{TSE} appendix survey, and (2) the actual number of clinically overt cases of foodborne cases of vCJD observed to date in the UK, France and the US and the absence of TTvCJD cases reported from France. It is clear to both FDA and UK authorities that the population of potentially vCJD-infected persons detected by the UK appendix survey (none of whom have been diagnosed with vCJD to date) must differ significantly from the population of 173 cases of overt vCJD (all of whom have died by the end of 2011). UK authorities responded by "calibrating" their risk assessments to accept the results of the appendix survey as possibly reflecting the true prevalence of latent vCJD infection but proposing several scenarios involving new assumptions (e.g. a small percentage of short incubation periods among infected

persons with the MM phenotype at PrP codon 129; or variable susceptibility to disease) that might explain the limited numbers of cases actually observed—an understandable precautionary approach, considering that the UK must confront a worst-case scenario in which many blood recipients may have already been exposed to the vCJD agent and others might be exposed in future transfusions. FDA's approach to resolution of the same inconsistency consisted in provisionally concluding that the possible worst-case prevalence (based on the UK appendix survey) is less likely than the substantially lower prevalence (based on clinical modeling of the UK epidemic), because the lower prevalence remains more consistent with cases observed to date. FDA nonetheless considers it prudent to keep an open mind about the true prevalence of latent vCJD infections in the UK and therefore potentially in the US. Biological explanations for this discrepancy, while credible, are speculative at this time. Also, we await a future determination of the specificity of the immunohistochemical test for PrP^{TSE} used in the UK appendix survey (a major technical limitation of which has been a lack of control appendix samples from a low-risk population). FDA also intends to run the model using assumptions modified as suggested by the UK scenarios.

Conclusions

For U.S. blood donors, the FDA model assumes that the major source of vCJD risk is dietary exposure during travel or residence in the U.K., France, or other countries in Europe since 1980. Donor deferral criteria, in place since 1999, are believed to have removed approximately 80% of the risk from donations by vCJD-infected persons. However, some infected donors are probably not deferred and might donate an RBC unit that could potentially transmit vCJD to a recipient. The FDA risk assessment model provides only an approximate estimate of the vCJD risk to individual transfusion recipients and the recipient population as a whole. Analysis of the risk assessment model indicates that the largest amount of inherent uncertainty comes from the estimate of U.K. vCJD prevalence. Based upon a comparison of the results of the high and low prevalence risk estimates with the current epidemiology of symptomatic vCJD infection, and taking into consideration current scientific uncertainty regarding the significance of the U.K. appendix data, FDA believes that the low prevalence risk model is more likely than the high risk model to be predictive of the risk of TTvCJD in the U.S. This supports the interpretation that the risk of vCJD from red blood cells in the U.S. is likely to be very small. However, given the current state of TSE science, estimates of the probability of vCJD infection or illness arising from exposure to the vCJD agent are still highly uncertain. This risk assessment nonetheless provides a platform for discussion of the research needed to improve model-based estimates of risk, evaluation of risk control measures, as well as risk communication that appropriately conveys the probabilities of the risks and the associated uncertainties.

Questions for the Committee

1. Does the Committee agree that the FDA Risk Assessment Model is structured appropriately?

   Please comment on any specific modifications to the model structure that FDA should consider.

2. Does the Committee agree with the inputs and assumptions used in the FDA Risk Assessment Model?

   Please consider any specific inputs or assumptions that FDA should consider.

3. Does the Committee agree that the validation exercises (predictions of primary vCJD case in the U.S. and TTvCJD cases in the U.K. and France) support FDA's conclusion that outputs of the FDA risk model based upon the low prevalence estimate of vCJD in the U.K. is likely to be more reliable than those based on the appendix survey?

4. Does the Committee agree with FDA's interpretation that the risk of TTvCJD in the U.S., while highly uncertain, is likely to be very small, based upon the results of the Risk Assessment Model in the context of other available evidence?

APPENDIX

Table A-1. Major input distributions used in exposure assessment model.

Variable name and description	Type of distribution or estimate used	Value and range	Reference
Prevalence estimates of vCJD in the UK 1. Low vCJD Case Prevalence ($Pv_{vCJD\text{-}UK:}$) 2 High vCJD Infection Prevalence ($Pv_{vCJD\text{-}UK:(20\text{-}30yrs)}$)	Triangular distribution Triangular distribution	Mean= 1.7 cases/million, 95% CI=0.2-3.7 cases/million Mean= 493 cases/million, 95%CI=282-801 cases/million	(Garske and Ghani, 2010) (Hilton, 2004; HPA, 2012)
RR_{UK}: Relative vCJD exposure risk in the UK	Point estimate	1	(Williams, 2004)
RR_{FR}: Relative vCJD exposure risk in the France	Point estimate	0.10	(Williams, 2004)
RR_{EU}: Relative vCJD exposure risk in the other countries in Europe	Point estimate	0.015	(Williams, 2004)
RR_{DOD}: Relative vCJD exposure risk in the US military bases in Europe	Point estimate	0.35	(Williams, 2004)
$N_{DR\text{-}US}$: Annual number of blood donations in the US	Normal distribution	Mean=17 million SD = 189,000	(HHS, 2009)
$P_{DR\text{-}US_a}$: Percentage of donors per US donor age group	Age specific percentage		(Forshee and Walderhaug, 2009)
$N_{DN\text{-}DY\text{-}US_d}$: Average number of donations per US blood donor per year	Age specific rate	Min=1, Mean=1.4, max=1.5	(HHS, 2009)
IP_{MM}: vCJD Incubation time for primary case with the MM genotype	Lognorm distribution	Median=12 years, 90%CI=9-35 years Mean=15 years	(Collinge et al., 2006; Garske and Ghani, 2010; Ghani et al., 2003)
IP_{MV}, IP_{VV}: vCJD Incubation time for primary case with the MV and VV genotype	Lognorm distribution	Median=32 years 90%CI=23-55 years Mean=35 years	(Collinge et al., 2006)
IP_{Infbl}: Percentage of late incubation period start having infectious agent present in blood	Triangular distribution	Min=50%, Most likely=75%, Max=90%	(Houston et al., 2008)
$Perc_{MM}$: Percentage of UK population who are MM genotype	Point estimate	40%	(Alperovitch et al., 1999)
$Perc_{MV}$: Percentage of UK population who are MV genotype	Point estimate	50%	(Alperovitch et al., 1999)
$Perc_{VV}$: Percentage of UK population who are VV genotype	Point estimate	10%	(Alperovitch et al., 1999)
R_{SC}: Efficiency of US donor screening	Uniform	Min=85%, Max=99%	(TSEAC, 2005)
$N_{TF\text{-}US}$: Annual number of blood transfusions in the US (million)	Normal distribution	Mean=3.8 million, 95%CI= 3.5-4.0	(Anderson et al., 2007; HHS, 2009)
$N_{U\text{-}TF\text{-}US}$: Number of blood units per transfusion in the US	Empirical discrete distribution	95%CI=3.8-4.0	(Anderson et al., 2007)
ID: Infectious doses in RBC unit	Triangular distribution	Min=0.56, Mean=0.75, Max=0.96	(Gregori et al., 2011)
IS_{MM}: vCJD Incubation time for secondary transfusion-transmitted case with the MM genotype	Triangular distribution	Min=6 years, mean=10 years and Max=20 years	(Bennett P and Daraktchiev M, 2011)
IS_{MV}, IS_{VV}: vCJD Incubation time for secondary transfusion-transmitted case with the MV and VV genotype	Triangular distribution	Min=16 years, mean=20 years and Max=30 years	(Bennett P and Daraktchiev M, 2011)
S_{uv}: Post-transfusion survival rate	Function of number years after transfusion ($Year_{post\text{-}transfusion}$)	0.61 - 0.028 x $Year_{post\text{-}transfusion}$	Regression model derived from UK data (Bennett P and Daraktchiev M, 2011)

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医薬品　研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
一般的名称	－		研究報告の公表状況	http://ansm.sante.fr/S-informer/Informations-de-securite-Retraits-de-lots-et-de-produits/Medicaments-Derives-du-Sang-LFB-Biomedicaments-Rappel-de-lots2	公表国：仏国	
販売名（企業名）	－					

研究報告の概要

LFB Biomedicament は仏 ANSM（医薬品・保健製品安全庁）との同意の下、散発性クロイツフェルト・ヤコブ病を発症した可能性のある患者の血漿から製造された Vialebex（albumine humaine：human albumin）のロット 12L01105（使用期限 2013 年 4 月，CIP コード 3400956446827）とロット 12L01291（使用期限 2013 年 10 月，CIP コード 3400957010782）を回収している。
この回収は予防的措置であり、本件による散発性クロイツフェルト・ヤコブ病感染の報告は受けておらず、また、血液製剤の製造過程においてプリオン除去に効果的とされている処理が含まれている。
血液製剤による散発性クロイツフェルト・ヤコブ病の感染は、現時点での科学的知見によれば理論上のリスクであって、新たに証明され特定されたリスクではない。

報告企業の意見	今後の対応
仏国における散発性 CJD に起因するアルブミン製剤の回収に関する情報である。 理論上のリスクであって、新たに証明され特定されたリスクではないとのことである。 なお、当社血漿分画製剤はフランス由来の原料血漿を用いていない。	今後ともプリオン病に関する安全性情報等に留意していく。

使用上の注意記載状況・その他参考事項等

重要な基本的注意
現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

文献番号 12

Médicaments Dérivés du Sang - LFB Biomédicaments - Rappel de lots

06/03/2013
MED13 / B006

Le laboratoire LFB BIOMEDICAMENTS procède, à la demande de l'ANSM, au rappel des lots des médicaments dérivés du sang (MDS) mentionnés ci-après issus du plasma d'un donneur de sang ayant développé un cas probable de maladie de Creutzfeldt-Jakob sous sa forme sporadique.

Ce rappel est effectué par mesure de précaution dans le cadre de la politique de sécurité transfusionnelle.

Aucun cas de transmission de la forme sporadique de la maladie de Creutzfeldt-Jakob par les MDS n'a été rapporté. En outre, les procédés de fabrication des MDS comportent des étapes considérées comme efficaces pour l'élimination des prions.

Conformément à la circulaire DGS/SQ4n°98/231 du 9 avril 1998, un tel rappel n'appelle pas une information nominative, telle que prévue par l'article L 1111-2 du code de la santé publique, des patients ayant reçu les produits des lots concernés par le rappel. En effet, la transmission par les médicaments dérivés du sang de la forme sporadique de la maladie de Creutzfeldt-Jakob constitue en l'état actuel des connaissances scientifiques un risque théorique et non pas un risque nouveau avéré et identifié.

Liste des lots concernés par le rappel LFB BIOMEDICAMENTS du 6 mars 2013 :

- Vialebex 40 mg/ml - 20g/500 ml - Code CIP 3400956446827
  Lot :12L01105 (Exp : 04/2013)
- Vialebex 50 mg/ml – 25g/500 ml - Code CIP 3400957010782
  Lot : 12L01291 (Exp : 10/2013

血液製剤――LFB Biomédicaments 社――ロットリコール

LFB Biomédicaments 社の研究所は、ANSM（医薬品・保健製品安全庁）からの要請に基づき、以下に記述する血液製剤ロットのリコールを実施する。対象となるのは、散発性クロイツフェルト・ヤコブ病の発症が疑われる血液提供者の血漿に由来するロットである。

このリコールは、輸血安全指針の枠組みに基づき、慎重を期して実施されるものである。

血液製剤による散発性クロイツフェルト・ヤコブ病の感染は一切報告されていない。またこれに加え、血液製剤の製造方法にはプリオン除去に有効であると考えられる段階が含まれている。

1998 年 4 月 9 日付通達 DGS/SQ4 第 98/231 号によれば、この種のリコールは、公衆衛生法典第 L. 1111-2 条に定めるような、リコール対象ロットの製品を投与された患者個人に対する情報提供を要するものではない。実際のところ、血液製剤による散発性クロイツフェルト・ヤコブ病の感染は、現時点での科学的知見によれば理論上のリスクであって、新たに証明され特定されたリスクではない。

別紙様式第2-1

No. 16

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2013. 3. 12	該当なし	

一般的名称	解凍人赤血球濃厚液	研究報告の公表状況	Johnson ST, Van Tassell ER, Tonnetti L, Cable RG, Berardi VP, Leiby DA. Transfusion. 2013 Feb 27. doi: 10.1111/trf.12125. [Epub ahead of print]	公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社) 解凍赤血球液-LR「日赤」(日本赤十字社) 照射解凍赤血球液-LR「日赤」(日本赤十字社)			米国

研究報告の概要

○コネチカット州の供血者における*Babesia microti*のリアルタイムPCR検査:スクリーニングアルゴリズムの意義

背景: *Babesia microti*は、輸血感染の可能性がある赤血球内原虫である。コネチカット州における*B.microti*の血清陽性率は約1%であるが、供血者における原虫血症の割合は不明であり、感染のリスクが懸念されることから、コネチカット州の*B.microti*が流行している地域の供血者における*B.microti* DNAの陽性率を調べ、また、同時に行ったIFA検査による抗体検出結果と比較した。

研究デザインと方法: 2009年8月中旬～10月初旬、コネチカット州南東部の同意を得た供血者から血液サンプルを採取し、IFAでIgG抗体を、リアルタイムPCRで*B.microti* DNAを調べた。

結果: コネチカット州の供血者1,002人中25人(2.5%)がIFA陽性であり、3人(0.3%)がPCR陽性であった。3人のPCR陽性者のうち2人はIFAともに陽性であったが、1人はIFA陰性であり、ウィンドウ期であった可能性がある。

結論: *B.microti*流行地域において、IFA陰性者を含め、3人のリアルタイムPCR陽性供血者を前方視的に確認した。この結果は、感染能を有する全供血者を同定するには抗体検査のみでは不十分であり、少なくとも*B.microti*の媒介昆虫であるダニが増える季節中は、ウィンドウ期の感染を検出する核酸検査を含めた検査アルゴリズムをより明確に定義する必要性を示している。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-LR「日赤」
解凍赤血球液-LR「日赤」
照射解凍赤血球液-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
米国コネチカット州の*Babesia microti*流行地域の供血者において、前方視的に*B.microti*のリアルタイムPCR検査を行ったところ、IFA陰性者を含む3人(0.3%)のPCR陽性者が確認され、*B.microti*の輸血感染低減戦略には核酸検査を含める必要があるとの報告である。	日本赤十字社では問診時にバベシア症の既往を確認し、該当する場合は献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

MedDRA/J Ver.16.0J

文献番号 13

ORIGINAL ARTICLE

Babesia microti real-time polymerase chain reaction testing of Connecticut blood donors: potential implications for screening algorithms

Stephanie T. Johnson, Eric R. Van Tassell, Laura Tonnetti, Ritchard G. Cable, Victor P. Berardi, and David A. Leiby

BACKGROUND: *Babesia microti*, an intraerythrocytic parasite, has been implicated in transfusion transmission. *B. microti* seroprevalence in Connecticut (CT) blood donors is approximately 1%; however, it is not known what percentage of donors is parasitemic and poses a risk for transmitting infection. Therefore, we determined the prevalence of demonstrable *B. microti* DNA in donors from a highly endemic area of CT and compared observed rates with concurrent immunofluorescence assay (IFA) testing results.

STUDY DESIGN AND METHODS: Blood samples from consenting donors in southeastern CT were collected from mid-August through early October 2009 and tested by IFA for immunoglobulin G antibodies and real-time polymerase chain reaction (PCR) for *B. microti* DNA. IFA specificity was determined using blood donor samples collected in northwestern Vermont (VT), an area nonendemic for *Babesia*.

RESULTS: Of 1002 CT donors, 25 (2.5%) were IFA positive and three (0.3%) were real-time PCR positive. Among the three real-time PCR–positive donors, two were also IFA positive, while one was IFA negative and may represent a window period infection. The two IFA- and real-time PCR–positive donors appeared to subsequently clear infection. The other real-time PCR–positive donor did not provide follow-up samples. Of 1015 VT donors tested by IFA, only one (0.1%) was positive, but may have acquired infection during travel to an endemic area.

CONCLUSION: We prospectively identified several real-time PCR–positive blood donors, including an IFA-negative real-time PCR–positive donor, in an area highly endemic for *B. microti*. These results suggest the need to include nucleic acid testing in planned mitigation strategies for *B. microti*.

Babesia microti, an intraerythrocytic protozoan parasite transmitted by the black-legged tick (*Ixodes scapularis*), is the primary agent of human babesiosis in the United States. The white-footed mouse, *Peromyscus leucopus*, serves as the reservoir host for *B. microti*, while infection in humans is incidental and usually asymptomatic. However, certain populations, including the immunosuppressed, splenectomized, and/or elderly, are more likely to develop severe disease. Clinical manifestations of babesiosis may include fever, chills, sweating, myalgias, fatigue, hepatosplenomegaly, and hemolytic anemia.[1] During the past three decades, *B. microti* has emerged as a significant blood safety concern as asymptomatic blood donors can transmit the parasite through blood donation to susceptible blood recipients.[2] Indeed, *B. microti* has been implicated in more than 159 cases of transfusion-transmitted *Babesia* (TTB) since 1979.[3-5]

ABBREVIATIONS: ARC = American Red Cross; CCT = chaperonin-containing t-complex polypeptide; CT = Connecticut; ID = identification; IFA = immunofluorescence assay; TTB = transfusion-transmitted *Babesia*; VT = Vermont.

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TRANSFUSION **;**:**-**.

In 87% of the reported TTB cases, a donor residing in an endemic area was implicated as the source of infection.[3] However, donor follow-up in TTB case investigations does not frequently identify a parasitemic donor due to the length of time it takes for follow-up and clearance of infection by the donor.[6] A longitudinal study of seropositive donors by the American Red Cross (ARC) revealed that only 18 of 115 (21%) enrolled donors had evidence of parasitemia (i.e., *B. microti* DNA) when assessed on follow-up samples, but no polymerase chain reaction (PCR) testing was performed on the index donation (D.A. Leiby, unpublished data). These longitudinal investigations revealed that some seropositive donors demonstrated evidence of parasitemia for up to 8 months after enrollment. However, it is not known what percentage of donors have demonstrable *B. microti* DNA at the time of donation and consequently pose a risk for transmitting *Babesia* to blood recipients.

As part of an ongoing research study conducted in the Connecticut (CT) Region of the ARC (D.A. Leiby, unpublished data),[6,7] the seroprevalence of *B. microti* in blood donors has been established by indirect immunofluorescence assay (IFA) over a 10-year period as 1.1%.[8] The current study was designed to ascertain the frequency of parasitemic donors, as determined by prospective real-time PCR testing of donors from an area of CT previously identified as highly endemic for *B. microti* and compare the results to observed IFA titers. An additional goal of the study was to identify the presence of potential window period infections (i.e., IFA negative and real-time PCR positive) in blood donors. We anticipate that the results may have implications for future testing interventions designed to prevent TTB.

MATERIALS AND METHODS

Donor enrollment and sample collection

During the time frame from August 17 through October 12, 2009, blood donors from drives in Middlesex and New London Counties, CT, were selected for enrollment in the study. These counties were chosen because they were previously identified as having the highest seroprevalence rates for *B. microti* and therefore would likely be the most productive for identifying parasitemic donors.[8] Similarly, the collection dates were chosen because they occurred during the peak period of tick activity (May through July for nymphs, August through October for adults) thereby enhancing the likelihood of identifying parasitemic donors. Donors at selected blood drives were provided an information sheet that described *B. microti*, the research study, and the risks and benefits of participating. Donor consent was documented by the signature on the blood donation record and donors not wishing to participate remained eligible for blood donation. Blood samples were drawn from the predonation sample pouch of consenting eligible donors using ethylenediaminetetraacetic acid (EDTA) tubes, and the samples were subsequently tested by IFA and real-time PCR for *B. microti*. Positive donors, by either or both tests, were notified by letter and/or phone of test results and that they would be deferred for an indefinite period, and associated blood products were discarded. All aspects of this study were reviewed and approved by the ARC's Institutional Review Board.

For the purposes of IFA specificity determination,[9] blood donors from drives in several Vermont (VT) counties surrounding Burlington (Grand Isle, Franklin, Lamoille, Washington, and Addison) were enrolled in the study from May 18, 2009, through September 10, 2009. Northwestern VT counties were chosen because the population was expected to have limited exposure to *B. microti* based on the absence of *Babesia* case reports from this region to the VT State Health Department and geographic and climatic conditions (i.e., high elevation and noncoastal area) that we considered unfavorable for survival of the parasite.[10] The proximity of the neighboring counties to the ARC's Burlington Blood Center allowed for timely shipment of EDTA blood samples for testing. Consent, notification, and deferral of donors and the disposal of associated blood products were performed as described above.

Serologic testing

Serologic testing was performed using an IFA for immunoglobulin (Ig)G antibodies to *B. microti*, as per the manufacturer's instructions (Focus Technologies, Inc., Cypress, CA), with a positive titer cutoff of at least 64. In general, IFA testing for *B. microti* utilizes slide wells coated with *B. microti*–infected hamster red blood cells as the antigen source. Briefly, plasma samples obtained from EDTA collection tubes were diluted 1 to 64 in phosphate-buffered saline (PBS) and 20 µL was added to each slide well containing fixed *B. microti* antigen and incubated at 37°C for 30 minutes in a humid chamber. After incubation, slides were washed for 10 minutes in PBS by agitation, rinsed in distilled water, and air-dried. Diluted fluorescein-labeled goat anti-human IgG conjugate (Focus Technologies) was added to each well and again incubated at 37°C for 30 minutes in a humid chamber. Slides were then washed for 10 minutes in PBS by agitation, rinsed in distilled water, and air-dried. Samples were examined by fluorescence microscopy at 400× magnification, considered positive at 64 or greater, and titered to endpoint. Appropriate negative and positive controls were included in all IFA testing. Samples were aliquoted, labeled with a study identification (ID) and sent to Imugen, Inc. (Norwood, MA) for real-time PCR testing.

Real-time PCR testing

Testing for *B. microti* DNA was performed at Imugen, Inc., using a real-time fast PCR method employing primers and

labeled probes targeting the *B. microti* 18S ribosomal RNA gene.[11] DNA was extracted from whole blood utilizing an automated magnetic bead–based isolation and purification system. Controls for each amplification plate within a run consisted of a template negative, a high template count, a low template count, and a reagent control. Results were considered positive if *B. microti* DNA amplification was repeatedly detected (CT ≤ 45) in one or more PCR amplifications from a replicate extraction of the donor blood sample.

To control for environmental amplicon contamination, *B. microti* 18S PCR–positive whole blood samples were reextracted and retested by real-time PCR employing primers and labeled probes coding for the chaperonin-containing t-complex polypeptide (CCT), a template not previously targeted or amplified in the testing facility. A positive finding was defined as amplification (CT ≤ 45) in one or more replicate extractions. Further technical details of the assays are proprietary.

Statistical analysis

Statistical comparisons were performed utilizing the chi-square and/or Fisher's exact tests. A p value of less than 0.05 was considered significant.

RESULTS

A total of 1002 CT blood donors were tested by IFA and real-time PCR for evidence of exposure to *B. microti*; 25 (2.5%) tested positive by IFA, while three (0.3%) tested positive by real-time PCR and were confirmed when retested by the CCT real-time PCR (Table 1). Two of the three real-time PCR–positive donors were also IFA positive, while one real-time PCR–positive donor was IFA negative. Nine of the 26 (34.6%) donors that were found positive by either IFA and/or real-time PCR had previously tested negative by IFA through the earlier seroprevalence study. A total of 25 previous samples were collected from these nine donors; the number of samples from each donor ranged from one to six. Two of these nine donors had tested seronegative just 16 weeks before their positive test result, while the seronegative status for the remaining seven donors was last documented 1.5 to 7 years previously (Table 2).

Six (2.3%) seropositive donors, of 261 tested, were identified in August, and 17 (2.8%), of 607, in September, but only two (1.5%), of 134, in October. All three real-time PCR–positive donors were identified in samples collected on or before September 1 (Fig. 1). Of the 1002 donors tested, 55% were male and the age range of the seropositive donors was 18 to 76 years old, with a median age of 46; seronegative donors ranged from 17 to 84 years old, with a median age of 48. Ten of 447 (2.2%) female donors tested were seropositive and 15 of 555 (2.7%) male donors were seropositive. There were 111 first-time donors tested and four (3.6%) were seropositive, while 891 repeat donors were tested and 21 (2.4%) were seropositive. Although blood drives selected for this study were held only in Middlesex and New London Counties, CT, donors did not necessarily reside within these two counties. Fifteen percent (147/1002) of the donors that were tested resided outside the selected geographic area and accounted for 8% (2/25) of the seropositive donations. No significant differences were found when comparing any of these groups by serostatus (i.e., seropositive vs. seronegative).

TABLE 1. Date of collection, IFA titer, and real-time PCR results for *B. microti*–seropositive donations

Date of collection	IFA titer	Real-time PCR	CCT real-time PCR*
08-17-2009	1:256	Positive†	Positive
08-25-2009	1:1024	Negative	
08-25-2009	1:64	Negative	
08-25-2009	1:256	Positive‡	Positive
08-26-2009	1:64	Negative	
08-27-2009	1:128	Negative	
09-01-2009	1:64	Negative	
09-01-2009	1:128	Negative	
09-01-2009	1:64	Negative	
09-01-2009	1:64	Negative	
09-01-2009	1:128	Negative	
09-01-2009	1:128	Negative	
09-01-2009	<1:64	Positive§	Positive
09-09-2009	1:64	Negative	
09-09-2009	1:64	Negative	
09-09-2009	1:128	Negative	
09-16-2009	1:256	Negative	
09-16-2009	1:256	Negative	
09-16-2009	1:512	Negative	
09-22-2009	1:128	Negative	
09-23-2009	1:128	Negative	
09-29-2009	1:256	Negative	
09-29-2009	1:64	Negative	
09-30-2009	1:64	Negative	
10-05-2009	1:64	Negative	
10-12-2009	1:64	Negative	

* CCT real-time PCR was only performed on samples identified as positive by standard real-time PCR.
† Sample ID 09-0922.
‡ Sample ID 09-0926.
§ Sample ID 09-0936.

Of the two IFA-positive and real-time PCR–positive blood donors, the first was a 44-year-old female repeat blood donor, while the second was a 70-year-old male repeat blood donor. Based on subsequent follow-up testing, both donors lost their real-time PCR–positive status 6 to 7 weeks after the index donation, but were documented to remain IFA positive for 4 to 6 months, after which time their antibody titers returned to baseline (Fig. 2). The third real-time PCR–positive donor, a 57-year-old male repeat donor, was IFA negative; however, we were unable to obtain follow-up samples from this donor.

A total of 1015 blood donors from northwestern VT counties were tested during the study period with one

TABLE 2. Previous IFA test results for nine IFA- and/or real-time PCR–positive donors

Study ID	Registration date	IFA titer	*Babesia* IFA test	*Babesia* real-time PCR
09-0922	8/2/2004	NA	Negative	NA
	8/17/2009	256	Positive	Positive
09-0926	6/18/2001	NA	Negative	NA
	9/5/2001	NA	Negative	NA
	8/2/2004	NA	Negative	NA
	12/27/2005	NA	Negative	NA
	2/27/2006	NA	Negative	NA
	2/25/2008	NA	Negative	NA
	8/25/2009	256	Positive	Positive
09-0927	6/11/2002	NA	Negative	NA
	10/7/2002	NA	Negative	NA
	8/26/2009	64	Positive	Negative
09-0929	10/9/2001	NA	Negative	NA
	9/27/2004	NA	Negative	NA
	11/29/2004	NA	Negative	NA
	11/14/2005	NA	Negative	NA
	5/12/2009	NA	Negative	NA
	9/1/2009	64	Positive	Negative
09-0931	5/2/2003	NA	Negative	NA
	9/1/2009	64	Positive	Negative
09-0936	7/29/2003	NA	Negative	NA
	7/29/2004	NA	Negative	NA
	9/27/2004	NA	Negative	NA
	11/29/2004	NA	Negative	NA
	7/8/2008	NA	Negative	NA
	5/12/2009	NA	Negative	NA
	9/1/2009	<64	Negative	Positive
09-0939	10/7/2002	NA	Negative	NA
	5/29/2007	NA	Negative	NA
	9/16/2009	256	Positive	Negative
09-0942	11/21/2006	NA	Negative	NA
	9/22/2009	128	Positive	Negative
09-0944	10/7/2003	NA	Negative	NA
	9/29/2009	256	Positive	Negative

(0.1%) testing IFA positive. When questioned at follow-up, it was determined that every summer this donor regularly traveled to Cape Cod, Massachusetts, an area known to be endemic for *B. microti*, and had visited as recently as 2 weeks before her IFA-positive blood donation. Thus, if this donor was actually infected by *B. microti* during previous travel to an endemic area, the IFA false-positive rate can be estimated as 0 in 1014 (0.00%; 95% confidence interval [CI], 0.00%-0.36%) with a specificity of 100%. However, if this donor was not infected during a prior visit, the estimated false-positive rate of the IFA was 1 in 1015 or 0.10% (95% CI, 0.00%-0.55%) with a specificity of 99.9%.

DISCUSSION

A total of 1002 CT blood donors were tested by IFA and real-time PCR; 25 (2.5%) tested positive by IFA and three (0.3%) tested positive by real-time PCR. The observed seroprevalence rate of 2.5% is similar to the 1.7% (185/10,970) seroprevalence rate previously reported for the same two CT counties (i.e., Middlesex, New London) over an 8-year study period.[8] The annual seroprevalence rate for *B. microti* in these two highly endemic counties has been consistent, remaining in a narrow range between 1.0 and 2.7% from 2000 through 2009. The three real-time PCR–positive donors identified in this study were found during the early part of the study period, all before September 1. *I. scapularis* nymphal ticks, the primary vector of human babesiosis, exhibit questing behavior and peak activity in the Northeast during May through July.[12,13] Thus, the detection of three acutely infected, and potentially parasitemic, donors appears to coincide with a period of peak nymphal tick activity. In contrast, a similar study conducted at Rhode Island Blood Center tested 2113 blood units from July 8, 2010, through June 30, 2011, and found 26 (1.2%) IFA positive, but reported no confirmed PCR results.[11] Thus, the current study is the first to prospectively identify the presence of PCR-positive blood donors in an area highly endemic for *B. microti*. These donors are likely parasitemic and potentially capable of transmitting the infection through blood donation.

To further characterize the natural history of *Babesia* infection in the real-time PCR–positive donors, we sought to collect subsequent samples for additional testing. Based on follow-up testing, the two donors that were IFA and real-time PCR positive lost their real-time PCR–positive status 5 to 7 weeks after their index donation, but were documented to remain IFA positive for 4 to 6 months. For both donors, antibody titers peaked (512) after apparent parasite clearance (demonstrated through real-time PCR–negative test results), after which time their titers returned to baseline (Fig. 2). This pattern of an increase in IFA titer with concomitant PCR positivity and subsequent clearance of the parasite followed closely by peak IFA titers, then a return to baseline levels, is a classic parasitologic or immunologic progression observed in related *Babesia* studies (D.A. Leiby, unpublished data). Presently, blood donors with a history of babesiosis are indefinitely deferred from future blood donation.[14] If and when a reentry protocol is established for *Babesia*, donors who have apparently cleared the infection based on negative IFA and real-time PCR test results should be considered for reentry. The observed infection and clearance patterns are in part dictated by the timing of the infection and subsequent sample collection. Thus, other donor samples in this study that were IFA positive, but real-time PCR negative, may represent earlier *Babesia* infections that are in the process of clearing and returning to baseline levels.

The single IFA negative and real-time PCR–positive donor suggests that a window period infection was identified.[15] Window period infections, regardless of the agent involved, have important implications for blood donor screening since in the absence of nucleic acid testing (NAT), undetectable antibody may lead to a false-negative test result if testing algorithms are dependent upon serology only.[16-18] NAT has been instrumental in the blood center for identifying early infections with viral agents, before seroconversion.[19-21] Although it is also possible this

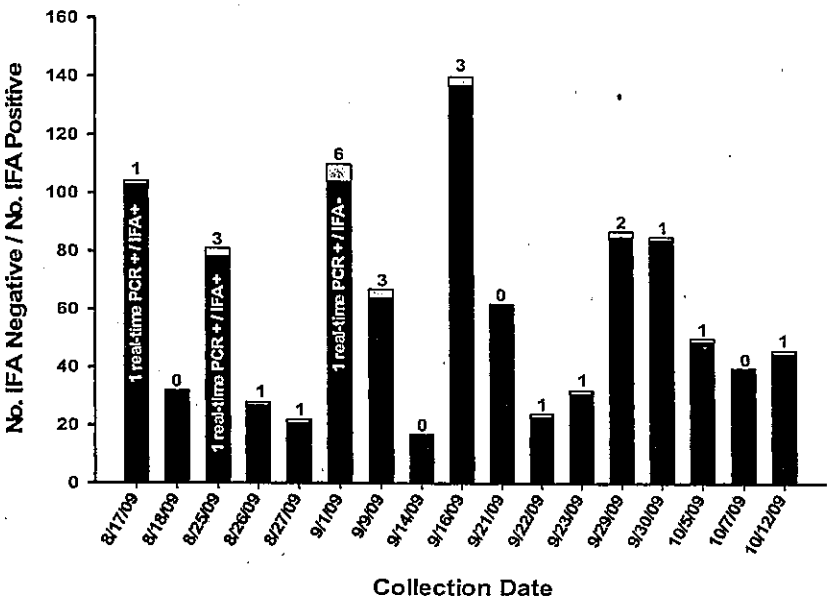

Fig. 1. Relationship of IFA-negative donors (■) to the number of IFA-positive donors (□) by date of collection. Numbers above bars represent the number of IFA-positive donors identified for the corresponding collection date. Collection dates for three donors identified as real-time PCR positive are designated by test results shown on the bar. Chronologically, the first two real-time PCR–positive donors were also IFA positive, while the last was IFA negative.

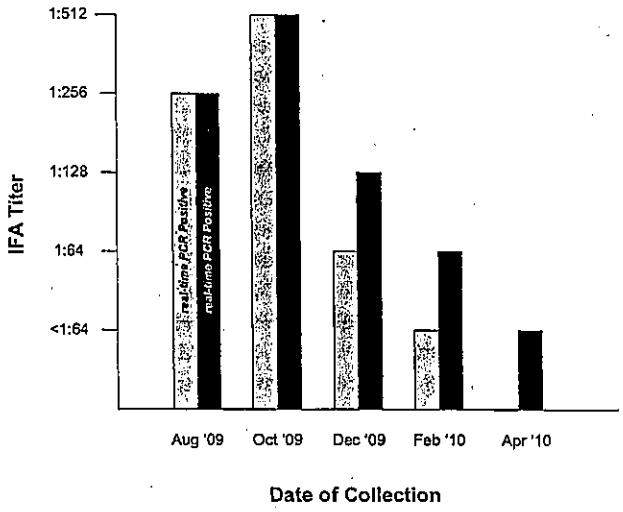

Fig. 2. Sequential IFA titers for follow-up samples collected from two IFA-positive donors identified as real-time PCR positive in August 2009. Subsequent samples were also tested by real-time PCR, but all were negative. (□) Study ID 09-0922; (■) Study ID 09-0926.

donor's test result may represent a real-time PCR false positive, the subsequent positive result when retested by the CCT real-time PCR does not support amplicon contamination as a contributing factor. Ideally this window period infection would have been validated by obtaining follow-up samples from the donor and demonstrating seroconversion;[15] unfortunately subsequent samples were not available. Window period infections have important implications for *B. microti* testing algorithms which may require NAT, in addition to IFA, during the tick season.

As already discussed, the observed seroprevalence rate of 2.5% for Middlesex and New London Counties is similar to historical testing data for these two counties. Further validation of the positive IFA results was obtained by testing of donors in northwestern VT, an area considered to be nonendemic for *B. microti*, where significantly fewer, one of 1015 (0.1%), donors were IFA positive. While the lone positive donor reported risk factors that suggest a true infection and a false-positive rate of zero, one could alternatively argue this infection represents a false positive. Based on the latter scenario, we can estimate the false-positive rate of the IFA test as only 1 of 1015 (0.10%) with a specificity of 99.9%, thereby supporting the observed seroprevalence rates in the highly endemic counties of CT.

Inherent to this study are several limitations. The foremost limitation is the relatively small sample size (n = 1002) of participating donors. Additionally, the study was conducted toward the end of the active tick biting season, specifically mid-August through early October. Taken together, these two factors likely had a negative influence on the number of donors identified as real-time PCR positive, leading to a conservative estimate of new infections, including identification of potential window period infections. In addition, no information is available on window period infections outside of the tick season since we only tested donors during periods of peak tick

activity. As already discussed, the inability to obtain follow-up samples from the single IFA-negative and real-time PCR–positive donor limited our ability to verify this possible window period infection. Further investigation is needed to better define the prevalence of presumptively parasitemic donors at the time of donation, both during and outside of the active tick season.

In summary, the current study documents the presence of parasitemic donors (0.3%) during the tick season in CT and suggests the presence of potential window period infections (0.1%). This supports the need for a clearly defined testing algorithm, including a NAT to detect window period infections at least during the tick biting season, as antibody testing alone may not be sufficient to identify all infectious blood donors. Additional studies involving a greater number of samples will help to further define a suitable testing algorithm; however, it is clear that an intervention is needed to mitigate TTB.

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CONFLICT OF INTEREST

SJ, EVT, LT, RC, and DL have no conflict of interest. VB is an employee of Imugen, Inc.

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医薬品　研究報告　調査報告書

<table>
<tr><td>識別番号・報告回数</td><td colspan="2"></td><td>報告日</td><td>第一報入手日
2013年4月15日</td><td>新医薬品等の区分
該当なし。</td><td rowspan="3">総合機構処理欄</td></tr>
<tr><td>一　般　的　名　称</td><td colspan="2">別紙のとおり。</td><td rowspan="2">研究報告の
公表状況</td><td rowspan="2">Clin Infect Dis,2013;April 12
DOI:10.1093/cid/cit177</td><td rowspan="2">公表国
米国</td></tr>
<tr><td>販売名（企業名）</td><td colspan="2">別紙のとおり。</td></tr>
<tr><td>研究報告の概要</td><td colspan="5">問題点：米国で、輸血によるエールリッヒア症伝播の可能性が初めて示唆された。

2011年夏、Georgiaの9歳の男児が輸血によりエールリッヒア症を発症し、米CDCによれば、輸血によるエールリッヒア症伝播の可能性が初めて示されたとのこと。男児は急性リンパ性白血病のため屋外で活動することはなく、家族によればダニから感染する要因は思いつかないとのことである。男児は化学療法により貧血となり、前の月に3回の輸血を受けた後、発熱、嘔吐および発疹が発生しただためがん専門医を受診した。様々な可能性の中で、最終的に病理学者が核酸増幅検査により原因菌を特定し、doxycyclineの投与によって速やかに軽快した。
保健当局は、男児へ輸血された輸血製剤のドナー3名は全員エールリッヒア症の症状を有していなかったものの、その内の1名がエールリッヒア菌に対する抗体を有していることを特定した。エールリッヒア菌に対する抗体を有するドナー由来の輸血製剤を投与された患者8名の内、3名はエールリッヒア症とは無関係な原因で死亡しており、残る5名はエールリッヒア症に係る検査で陰性であった。</td><td rowspan="3">使用上の注意記載状況・
その他参考事項等

記載なし。</td></tr>
<tr><td colspan="3">報告企業の意見</td><td colspan="2">今後の対応</td></tr>
<tr><td colspan="3">別紙のとおり。</td><td colspan="2">今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。</td></tr>
</table>

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文献番号　14

別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免役グロブリン、⑤人免役グロブリン、⑥乾燥ペプシン処理人免疫グロブリン、⑦乾燥スルホ化人免疫グロブリン、⑧乾燥スルホ化人免疫グロブリン、⑨乾燥スルホ化人免疫グロブリン、⑩乾燥スルホ化人免疫グロブリン、⑪乾燥スルホ化人免疫グロブリン*、⑫乾燥濃縮人活性化プロテインC、⑬乾燥濃縮人血液凝固第Ⅷ因子、⑭乾燥濃縮人血液凝固第Ⅷ因子、⑮乾燥濃縮人血液凝固第Ⅷ因子、⑯乾燥濃縮人血液凝固第Ⅸ因子、⑰乾燥濃縮人血液凝固第Ⅸ因子、⑱乾燥濃縮人血液凝固第Ⅸ因子、⑲乾燥抗破傷風人免疫グロブリン、⑳抗 HBs 人免疫グロブリン、㉑トロンビン、㉒フィブリノゲン加第ⅩⅢ因子*、㉓フィブリノゲン加第ⅩⅢ因子、㉔乾燥濃縮人アンチトロンビンⅢ、㉕ヒスタミン加人免疫グロブリン製剤、㉖人血清アルブミン*、㉗人血清アルブミン*、㉘乾燥ペプシン処理人免役グロブリン*、㉙乾燥濃縮人アンチトロンビンⅢ
販売名（企業名）	①献血アルブミン 20 “化血研”、②献血アルブミン 25 “化血研”、③人血清アルブミン “化血研” *、④ガンマーグロブリン筋注 450mg/3mL「化血研」、⑤ガンマーグロブリン筋注 1500mg/10mL「化血研」、⑥献血グロブリン注射用 2500mg「化血研」、⑦献血ベニロンーⅠ静注用 500mg、⑧献血ベニロンーⅠ静注用 1000mg、⑨献血ベニロンーⅠ静注用 2500mg、⑩献血ベニロンーⅠ静注用 5000mg、⑪ベニロン*、⑫注射用アナクトC2,500 単位、⑬コンファクトF注射用 250、⑭コンファクトF注射用 500、⑮コンファクトF注射用 1000、⑯ノバクトM静注用 400 単位、⑰ノバクトM静注用 800 単位、⑱ノバクトM静注用 1600 単位、⑲テタノセーラ筋注用 250 単位、⑳ヘパトセーラ筋注 200 単位/mL、㉑トロンビン “化血研”、㉒ボルヒール*、㉓ボルヒール組織接着用、㉔アンスロビンP500 注射用、㉕ヒスタグロビン皮下注用、㉖アルブミン 20%化血研*、㉗アルブミン 5%化血研*、㉘静注グロブリン*、㉙アンスロビンP1500 注射用
報告企業の意見	エールリッヒア症は、主にダニにより媒介されるエールリッヒア属のグラム陰性細菌を原因とした感染症であり、発熱、頭痛、筋肉痛等の症状を示すと共に、死亡例も報告されている。 今回の報告は、輸血によるエールリッヒア症伝播の可能性が初めて示されたことに関する報告である。 上記製剤の製造工程には、孔径約 0.2μm の無菌ろ過工程が導入されており、その効果はバクテリアチャレンジテストにより確認されている。また、上記製剤の製造工程には細菌より小型であるウイルスの除去を目的としたウイルス除去膜ろ過工程も導入されており、その効果は「血漿分画製剤のウイルスに対する安全性確保に関するガイドライン（医薬発第 1047 号、平成 11 年 8 月 30 日）」に基づく、モデルウイルスを用いたウイルスプロセスバリデーションにより確認されている。更に、これまでに上記製剤によるエールリッヒア症の感染報告例は無い。 以上の点から、上記製剤はヒトのエールリッヒア症に対する安全性を確保していると考える。

*：現在製造を行っていない

A Confirmed *Ehrlichia ewingii* Infection Likely Acquired Through Platelet Transfusion

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Ehrlichiosis is a tick-borne disease that ranges in severity from asymptomatic infection to fatal sepsis. Ehrlichiosis acquired from transfusion of blood products has not been documented in the literature to date. A case of *Ehrlichia ewingii* infection likely transmitted by transfusion of leukoreduced platelets is described, and public health implications are discussed.

Keywords. ehrlichiosis; transfusion; tick-borne; leukoreduction.

In mid-July 2011, a 9-year-old Georgia boy with a history of acute lymphoblastic leukemia and anemia secondary to chemotherapy presented to his oncologist complaining of fever, fatigue, malaise, vomiting, diarrhea, and petechial rash. He was admitted to the hospital, where cultures were performed and broad-spectrum antibiotics started to cover potential causes of sepsis. Despite antibiotic therapy, the patient's clinical status deteriorated with worsening neutropenia, thrombocytopenia, and elevated liver enzymes. On the 11th day of symptoms, the hospital laboratory identified morulae in granulocytes on a peripheral blood smear. The patient was immediately started on doxycycline and samples were sent to Mayo Clinic for testing. Real-time polymerase chain reaction (PCR) at Mayo Clinic was positive for *Ehrlichia ewingii* [1], which was confirmed by further PCR testing and sequence analysis at the Centers for Disease Control and Prevention (CDC) [2]. The boy became afebrile within 48 hours of doxycycline initiation, rapidly improved, and was discharged.

Although about 32% of patients with ehrlichiosis do not recall a recent tick bite [3], this case was unusual in that the patient's family also denied recent outdoor activity or animal contact due to the child's illness. In addition, the patient had multiple transfusions in the month preceding symptom onset. Therefore, a possible transfusion-acquired infection was suspected, prompting the physician to contact the blood bank and the CDC. When the products the child had received were determined to come from Florida, the Florida Department of Health was notified and the Florida blood bank involved conducted trace-back investigations on the 3 donors.

The 3 transfusion products that the patient received in the month prior to onset of his illness are documented in Figure 1. All products were leukoreduced and irradiated. All 3 donors denied any symptoms of illness during the time of donation. However, 1 donor reported frequent tick attachment at his home in Florida and a wooded property in South Carolina in the month prior to donation. All 3 donors were tested by indirect immunofluorescence assay serology at the CDC, and only the donor that had reported tick exposure was positive, with an *Ehrlichia* species immunoglobulin G (IgG) titer of 1:512. This donor is considered the most likely source of the boy's *Erhlichia ewingii* infection.

The *Ehrlichia*-positive donor had regularly donated platelets or plasma collected by apheresis 1–2 times per month. He reported no febrile illnesses in the 2 months prior to and following the suspect donation. Routine complete blood counts performed by the blood bank at the time of each donation were normal. Trace-backs of other recipients receiving blood products from the positive donor between 12 May 2011 and 27 July 2011 were performed to assess if any additional recipients had symptoms relating to *E. ewingii*. Five recipients received leukoreduced platelets and 3 recipients received plasma from the donor (Figure 1). Three of the recipients died within 1–2 days of transfusion due to unrelated causes. The remaining 5 recipients reported no symptoms of illness associated with *E. ewingii*; 4 of the 5 patients agreed to be tested and were negative by *Ehrlichia* species serology. It should be noted that none of the 4

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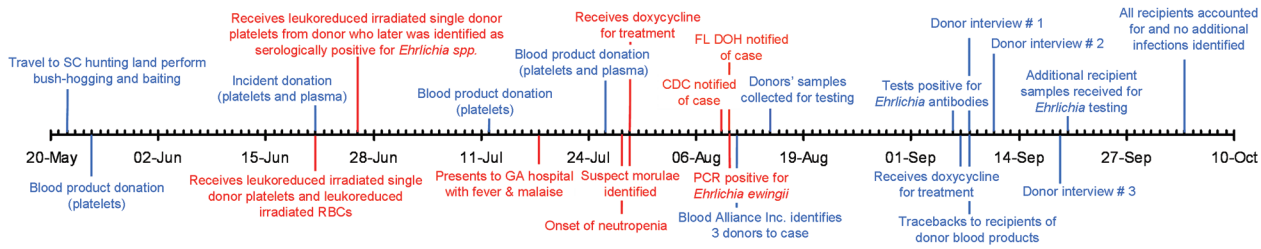

Figure 1. A timeline of the important case and donor events associated with the *Ehrlichia ewingii* transfusion-associated infection. The timeline begins with the donor's suspected tick exposure in May 2011 and ends with the completion of additional case trace-back investigations, October 2011. Abbreviations: CDC, Centers for Disease Control and Prevention; FL DOH, Florida Department of Health; GA, Georgia; PCR, polymerase chain reaction; RBCs, red blood cells; SC, South Carolina.

recipients who tested negative received products from the same donation date as the infected child.

There were no samples remaining from the incident donation, so confirmation of the donor's diagnosis through PCR was not possible. However, a significantly elevated *Ehrlichia* species IgG titer, such as the one found in the donor (1:512), is an uncommon finding [4, 5]. This, in addition to the child's reported lack of possible tick exposure, make transfusion the likely source of *E. ewingii* infection.

There are several unique aspects of this case that have public health importance. *Ehrlichia ewingii* belongs to a group of organisms in the family Anaplasmataceae, a group that also includes the tick-borne pathogens *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum*. These organisms reside in leukocytes, where they form clusters of organisms known as morulae that are sometimes visible by microscopy. Although it has been previously demonstrated that transfusion transmission of *Ehrlichia* species is scientifically plausible [6], this case report is the first documentation of likely occurrence in the literature. In contrast, there have been 5 published reports of *A. phagocytophilum* transmitted by transfusion of blood products [7–11].

The first 2 transfusion-transmitted *A. phagocytophilum* infections involved nonleukoreduced red blood cell transfusions [7, 11]. These initial reports, and the fact that these intracellular pathogens are typically found in leukocytes, encouraged speculation that leukoreduction may reduce the risk of transmission of pathogens in the family Anaplasmataceae. However, in 2012, 3 cases of transfusion-acquired anaplasmosis from leukoreduced blood products were reported [9, 10].

This is the first report of ehrlichiosis that was likely to have been acquired by transfusion, and the first to implicate leukoreduced platelets as the probable source of a tick-borne rickettsial pathogen. This suggests that, much like red blood cells, transfusion of platelets, even when leukoreduced, can transmit pathogens that are typically found in leukocytes. It should also be noted that the donation that was likely responsible for the transfusion-related infection was irradiated. Irradiation is not likely to kill the pathogen, or the leukocytes, but rather limits leukocyte reproduction. Physicians should be aware that irradiation or leukoreduction does not eliminate the risk of transfusion-acquired infection with this pathogen.

An additional unique aspect of this case is that the infection was confirmed to be due to a rarely reported species, *E. ewingii*, and not the more commonly reported *E. chaffeensis*. This pathogen was first documented as a cause of human disease in a 1999 publication by Buller et al [2]. Although *E. ewingii* infections may be symptomatic in immunocompetent individuals [12], a majority of published reports have occurred in people with some form of immune compromise [2, 13]. The most common symptoms in reported *E. ewingii* infections include fever, headache, and malaise, and thrombocytopenia and leukopenia may also be present [2].

Despite the relatively low number of reported cases, *E. ewingii* is likely widely distributed throughout the central and southeastern United States [14]. Given that serology does not distinguish between *E. ewingii* and *E. chaffeensis*, it is likely that some cases of *E. ewingii* infection are missed or misclassified as *E. chaffeensis* infections [2].

It is unclear at this time why both *A. phagocytophilum* and *E. ewingii* have now been implicated in transfusion infections, whereas *E. chaffeensis* has not. Unlike *E. chaffeensis*, which targets human monocytes, *E. ewingii* and *A. phagocytophilum* are usually found in granulocytes. There is no clear evidence that this affinity for granulocytes increases transfusion risk; however, granulocytes are typically more numerous in human blood than monocytes. It may be possible that granulocytes release more pathogen into the plasma prior to leukoreduction, or remain more prevalent in postleukoreduction products than monocytes. Another possible explanation is the relative severity of symptoms caused by the various pathogens. *Ehrlichia ewingii* ehrlichiosis, like anaplasmosis, has been documented to be less likely than ehrlichiosis caused by *E. chaffeensis* to result in severe or fatal outcome [13]. It may be possible that people who are infected with *E. chaffeensis* are less likely to remain

asymptomatic and present as donors than people infected with the more benign pathogens.

The previous reports of transfusion-transmitted anaplasmosis have described asymptomatic donors, and it appears from this case that it is also possible to remain asymptomatic during *E. ewingii* infection. This finding highlights the difficulty of preventing these pathogens from entering the blood supply. Even though our donor did recall extensive tick exposure, many people with tick-borne disease do not, and using tick exposure questions to screen potential donors is not only likely to miss cases, but also may substantially decrease the number of available donors in some regions [15]. At the present, screening all donated blood products by PCR for *Ehrlichia* species is cost prohibitive and of unknown utility [9]. Screening donors for symptoms of illness or abnormal laboratory findings such as thrombocytopenia would not have been useful in excluding this donor either. Therefore, at the present there is no screening method that can be practically implemented to prevent an asymptomatic infected donor from donating blood products. Early reporting of suspected transfusion-related infections to the blood collection agency and public health authorities is of key importance so that potentially infectious co-components may be tracked and quarantined and the infected donor and recipients can be treated.

Although in this case identification of morulae aided in making the initial diagnosis, the sensitivity of morulae detection in ehrlichiosis and anaplasmosis is low, and physicians usually need to treat the patient without confirmation of diagnosis. The recommended treatment for ehrlichiosis is doxycycline; other broad-spectrum antibiotics are not likely to be effective, and treatment delay can lead to adverse outcome or death [16]. Therefore physicians will need to consider this pathogen as a possibility early during treatment of possible transfusion-related infections and begin doxycycline treatment as soon as the disease is suspected. Given the challenges in confirmation of diagnosis, rapid empiric treatment is essential, and an astute physician is a patient's best defense.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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医薬品
医薬部外品　　研究報告　調査報告書
化粧品

別番号・報告回数			報告日	第一報入手日 2013 年 03 月 04 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	乾燥濃縮人アンチトロンビンⅢ		研究報告の公表状況	fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/2013/02/26	公表国 アメリカ	
販売名 （企業名）	①ノイアート静注用 500 単位　（日本血液製剤機構） ②ノイアート静注用 1500 単位　（日本血液製剤機構）					

研究報告の概要

業界のためのガイダンス（ドラフトガイダンス）
梅毒のスクリーニング試験に基づいた、血液ドナーと血液および血液成分のスクリーニング、試験、および管理のための勧告事項（ドラフトガイダンス）

このドラフトガイダンスはFDAのこの問題に関しての現在の考え方を示したものである。このガイダンスはいかなる人にも何らかの権利を与えたり新たな権利関係を生み出したりするものではなく、また、FDAもしくは公衆を拘束するために行おうとするものではない。ここに書かれたものとは別のアプローチも、もしその様なアプローチが、適用される法もしくは規則の要求するところに合致するならば、用いることができる。別のアプローチについて話し合いたいならば、本ガイダンスの実施を担当しているＦＤＡのスタッフにコンタクトせよ。適当なFDAスタッフが見つけられない場合には、本ガイダンスの表紙に書かれている番号に電話せよ。

Ⅰ．緒　　言

FDAは、全血もしくは血液成分(原料血漿を含む)を採取する血液採取・取扱施設に対して、梅毒のスクリーニング試験に基づいた、ドナーのスクリーニングと試験、およびドネーションの管理に関する改訂勧告事項をここに提示する。

本ドラフトガイダンスは、2003 年 6 月付の「梅毒のスクリーニング試験に基づいたドナーと製品の管理のための勧告事項(改訂版)」("Guidance for Industry: Revised Recommendations for Donor and Product Management Based on Screening Tests for Syphilis")(参照文献 1)というタイトルのFDAのドラフトガイダンスと置き換わるものであり、本ドラフトが最終版となった場合には、1991 年 12 月 12 日付のメモランダム「梅毒試験の結果に基づくドナーの不適格判定と製品の出荷に関する FDA 勧告事項の説明」(Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing)(参照文献 2)に取って代わるものとなる。

FDAのガイダンス文書は、このガイダンスを含め、法的に強制力のあるものではなく、FDAのある問題に対する現在の考え方を示したものであり、特別な規制や立法の必要性を示していない限りは、単なる勧告事項と見なすべきである。FDAのガイダンス中での"should"という語は、何ごとかを示唆もしくは勧告することを意味しており、要求しているものではない。

Ⅱ．背　　景

A．輸血－梅毒の伝播

梅毒は、スピロヘータであるTreponema pallidum(T. pallidum)が原因となって起こり、感染者との性的接触後に感染することが最も多い。また、梅毒は母から子へも伝播しうるものであり、また、まれではあるが、活動性の梅毒を有するドナーから血液もしくは血液成分の輸注によって伝播しうる(参照文献 3)。米国では、輸血によって伝播した梅毒の記録で最も新しいものは1966年に報告された1例である(参照文献 4)。血液ドナー全員を検査するようになったことが、輸血による梅毒伝播がなくなったことに役割を果たしてきたのかもしれない。輸血による梅毒伝播が低減した理由についての別の説明として考えうるものとして：ドナーからレシピエントへの直接輸血が行われないようになったこと；冷蔵保存された血液成分中ではT. pallidum(低温感受性の微生物)の不活化が起こること；一般人におけ

使用上の注意記載状況・その他参考事項等

2．重要な基本的注意

(1)本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-1抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohnの低温エタノール分画で得た画分から人アンチトロンビンⅢを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

る梅毒の率が低下し、それがドナー集団にも反映していること；スピロヘータ血症（梅毒感染の原因であるスピロヘータが血液中に存在すること）の期間中に病的状態のため血液ドナーが自分自身の判断でドネーションをやめること；梅毒感染者となるようなハイリスクの行動をとるドナー候補者（例えば、性交のためにお金、ドラッグ、もしくはその他の報酬を受け取る人）は、ドナー適格性スクリーニングプロセスを経て不適格となっていること；輸血のレシピエントとなる人々では抗生物質が広範囲に用いられていること；ならびに、レシピエントの梅毒を輸血によって伝播したものであると診断することが困難であること、が挙げられる（参照文献5）。しかし、これらの説明のいずれも、数値化されたり、適切にヴァリデートされたことはない。

現行のT. pallidumについての試験基準はTitle 21 Code of Federation (CFR) Part 610, Subpart E（伝播性疾患の原因物についての試験基準"Testing Requirements for Communicable Disease Agents"）の特に§610.40(i) (21 CFR 610.40(i))に、また原料血漿（Source Plasma）のドナーについては§640.45(21 CFR 640.45)に含まれている。FDAはこれまでに何回か、梅毒試験を継続的に行う必要性についてパブリックコメントを求めてきており、最近では、2007年11月8日付で「輸注を目的とした、もしくはさらに製造へと進めることを意図した、人血液および血液成分についての基準」("Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use")と題する規則案を出している（72 FR 63416）。FDAは現在、その規則案に対してのコメントをレビューしているところである。梅毒について、血液ドネーションを試験する（§610.40(i)）、ならびに原料血漿ドナーを試験する（§640.45）、という現行の基準は、現在も有効なものである。

ドナーの血清学的試験についての米国赤十字からの情報によれば、2007-2008年に米国赤十字で反復して同種輸血のドナーとなった人々のうち、324例で梅毒感染が見出され、この数字は同じ時期にHIV、HBV、HCV、およびHTLV感染が見出された反復同種輸血ドナーの数（それぞれ、92、47、127、および9例）よりも数倍多い（参照文献6）。いくつかの公表されている研究では（参照文献7から12）、梅毒が確認されたかもしくはその可能性が高い人から得た血液サンプル中のT. pallidumの核酸の存在もしくは不在を報告しているが、それらの研究では梅毒感染者の血液サンプル中にスピロヘータ核酸を検出しており、感染者のうちの何人かは無症状の潜伏感染であった。このことは、無症状の血液ドナーのうちの何人かはスピロヘータ血症を有している可能性を示唆している。そのような血液ドナーからのドネーションはレシピエントに梅毒を伝播させる可能性がある。

B. 血液および血液成分の梅毒試験

§610.40(i)では、血液採取・取扱施設は、血液の各ドネーションごとに梅毒について血清学的スクリーニング試験を行わなければならない、としている（脚注 1）。梅毒スクリーニング試験で繰り返し反応性（reactive）であったドナーは不適格としなければならず（§610.40(i)）、そのドナーが不適格となったことは通知されなければならない（21 CFR 630.6）。FDAはそのドナーが梅毒に感染していることを確認するさらなる試験は要求しない。§610.41(b)に従って、血液採取・取扱施設は、下記のIV.BおよびC節に記載のとおり、当該ドナーを再適格化するために追加試験を行うことができる。§610.40(h)(2)(vi)に従って、FDAは、梅毒のスクリーニング試験で反応性を示した血液および血液成分（原料血漿を除く）であって、そのドネーションをさらに十分かつ適切な試験法で試験し、その試験法ではスクリーニング試験での反応性が生物学的に見て偽陽性であることを示す場合には、その血液および血液成分の使用を許可し、それらには2つの試験結果の双方が表示されることとなる。

原料血漿にのみ適用される、梅毒試験に関するFDAの基準は次の通りである：

1. 血清学的試験の結果に関連した、採取、試験、および表示の現行基準は、§640.65、§640.67、および§606.21に記載されている。
2. FDAの規則では、原料血漿ドナーが最初に検診を受けた日か、もしくはプラスマフェレーシスを行った日のうちのいずれか早いほうの日に血液サンプルを採取すること、さらにその後少なくとも4ヶ月ごとに血液サンプルを採取し、それらのサンプルを梅毒について試験することを求めていることに留意せよ（§640.65(b)(1)(i)）。
3. FDAの規則はまた、梅毒の試験結果が反応性であったドナーは、下記の第4項および第5項に述べている場合以外は、そのドナーでの試験が非反応性（nonreactive）となるまで再度プラスマフェレーシスを行ってはならないことを求めている（§640.65(b)(2)(ii)）。

医薬品
医薬部外品　研究報告　調査報告書
化粧品

4. 規則では、梅毒スクリーニング試験で反応性であったが生物学的試験で偽陽性であったドナーがプラスマフェレーシスを行うことを、次の条件のもとに認めているが、その条件とは、そのドナーの記録が：(a)生物学的に偽陽性の結果と確認された当該の反応性であった血清学的試験を同定しており、かつ、(b)施設内の医師が、その偽陽性反応が、そのドナーの基礎疾患（その疾患があった場合には当該ドナーがプラスマフェレーシスプログラムに参加を認められない類いの疾患）によって偽陽性となったものではないと判定したことを示している場合である（§640.65(b)(2)(iii)）。
5. 規則ではまた、梅毒試験で反応性であったドナーから得た血漿を梅毒血清学的試験の陽性対照血清として用いるために、そのドナーがプラスマフェレーシスを行うことを、次の条件のもとに認めているが、その条件とは:(a)施設内の医師がドネーションすることを承認し、かつ、(b)当該ドナーの記録に、医師もしくはクリニックからの署名入りのステートメントが含まれており、そのステートメントで梅毒の治療が開始されており、プラスマフェレーシスプログラムを継続することが当該梅毒感染ドナーの治療を妨害したり、無効とすることはないであろうと明確に述べている場合である（§640.65(b)(2)(iv)）。
6. 梅毒の試験結果が反応性であったドナーから採取された血漿の表示は、§606.121(e)(5)(iv)に述べられているとおり適切に行わなければならない。

Ⅲ. 梅毒の血清学的アッセイの特性

梅毒の血清学的アッセイとしては2つの異なるタイプすなわち：(A)非トレポネーマアッセイ と (B)トレポネーマアッセイがある。

(A) 非トレポネーマアッセイ、例えば迅速血漿レアギン(RPR)試験法、性病研究所(VRDL)試験法や自動レアギン(ART)試験法などは、種々の組織中に存在するカルジオリピンと呼ばれる抗原に対する「レアギン」抗体を検出する非特異的試験である。カルジオリピンに対する抗体は、活動性の梅毒やその他のいくつかの状態を有する人の血清中に出現する。しかし、以前に梅毒に感染したことがあり、治療が成功を収めた人でカルジオリピンに対する抗体が長期間低レベルで維持される人もいることは留意すべきである；そのような人は“serofast”と分類される。
以前に梅毒に感染し治療が成功を収めた人の血清と血漿は、通例、その成功した治療後1年から2年間以上にわたって非トレポネーマ試験で反応性のままであることはない。従って、活動性または最近梅毒感染の治療を受けた人は非トレポネーマ試験では通例は反応性を示すが、感染していない人や、治療が成功を収めてから年月を経た人では、通常は非トレポネーマ試験では非反応性だが特異的抗体の反応性は保持している。
非トレポネーマアッセイは最近梅毒に感染した人を見つけ出すことには有用であり、また梅毒の進行や抗体療法に対する応答のモニターには有用である。非トレポネーマアッセイで反応性であった血清を特異的トレポネーマアッセイで再試験することは、活動性の梅毒感染を示す真の陽性結果を、他の状態による生物学的には偽陽性の結果と区別することにおそらく有用であろう。

(B) トレポネーマアッセイとしては、化学発光免疫法、酵素免疫法(EIA)、蛍光トレポネーマ抗体吸収(“absorbed)”法(FDA-ABS)、Treponema pallidum 微量血球凝集法(MHA-TPA)、および Treponema pallidum 粒子凝集法(TP-PA)が挙げられる。トレポネーマアッセイはトレポネーマに特異的な抗原に対する抗体の有無を試験するものである。トレポネーマアッセイは最近の梅毒感染、および時期的に離れた、以前の梅毒感染を見出すのに有用ではあるが、梅毒の進行のモニターや抗体療法への応答を見ることには有用ではない。いくつかの例外はあるが、特異的トレポネーマ抗体についての陽性試験結果は、その人が現在感染しているか、または治療が成功を収めて治癒したかにかかわらず、その人は生涯陽性のままである(参照文献13)。

非トレポネーマアッセイとトレポネーマアッセイは双方とも、感染性のあるトレポネーマそれ自体を検出するものではなく抗体を検出するものなので、どちらのアッセイでも梅毒感染の非常に初期の「ウインドウ期間」、すなわち感染が起こっているがトレポネーマ抗原に対して、もしくはカルジオリピンに対しての抗体がまだ出現していない期間の患者を高い信頼性で見出すことはできない。

1990年以前には、血液採取・取扱施設の多くはドナーの梅毒についてのスクリーニングに非トレポネーマ試験を用いており、その試験で反応性であったサンプルについて、その非トレポネーマ試験結果の特異性を調べるためにトレポネーマ試験を行っていた。1990年にCBER(Center for Biologics Evaluation and Research)は、T. pallidumに対する特異的抗体を検出する改変・自動化した微量血球凝集

試験に510(k)市販前届出を承認した。この新しいトレポネーマアッセイがドナースクリーニング用に用いられるようになってからは、それまでは非トレポネーマ試験の結果が非反応性であることに基づいてドネーションに適格であるとされてきた反復ドナーのうちのいくらかは、T. palidiumに対する特異的抗体を有していることが判明したためにドナー不適格となった。この試験法によって大多数の生物学的に偽陽性の非トレポネーマスクリーニング試験結果が排除され、その試験の使用によっても不適格とされるドナーの総数には全体として増加は起こらなかった(参照文献14および15)。多くの血液採取・取扱施設は現在では高いスループットを有する自動化トレポネーマアッセイを用いており、それらは梅毒のドナースクリーニング用としてFDAが承認したもので、例えば、化学発光免疫法、EIA、およびTP-PAが挙げられる。しかし、血液採取・取扱施設によっては、スクリーニング法として非トレポネーマアッセイのRPRを用い続けているところもある。したがって、FDAとしては、ドナーおよび血液と血液成分の管理のための勧告事項を、血液採取・取扱施設が非トレポネーマスクリーニング試験、トレポネーマスクリーニング試験のいずれを用いた状況も規定している。

梅毒のスクリーニング試験結果を、追加して行った梅毒試験の結果と区別するために、FDAは「反応性」("reactive")および「非反応性」("nonreactive")という用語をスクリーニング試験結果(非トレポネーマ試験、トレポネーマ試験の双方とも)に用い、「陽性」("positive")および「陰性」("negative")という用語は、スクリーニング用として用いられたものと同一の血液検体のサンプルについて、その後に行われたトレポネーマ試験(ドナーの再適格化のために用いられる試験)の結果を示す場合に用いることとする。試験キットの添付文書に従えば"indeterminate"(不確定)、"questionable"(疑わしい)、もしくは"equivocal"(あいまい)とされる試験結果については、本文書の目的から考えて、「反応性」もしくは「陽性」の試験結果に相当するものと判断すべきである。

記録にとどめる試験として非トレポネーマアッセイを用いてドナーをスクリーニングしている血液採取・取扱施設は、トレポネーマ診断試験をドナーカウンセリングや不適格とした後の再適格化の判断のために用いることができ、また、反応性のスクリーニング試験結果が生物学的には偽陽性であったことを示す目的にも用いることができる(§610.40(h)(2)(vi))。しかし、FDAはその他の場合の全てにおいて、梅毒についてドナーをスクリーニングするために用いる血清学的試験法は、そのような使用を意図したものとしてFDAによって承認された試験法とすべきことを勧告する(第IV.B節およびC節の勧告事項を参照せよ)。

IV. 梅毒についての試験を用いる場合の、ドナー試験と管理、および製品の処置に関する勧告事項

A. 梅毒の病歴を有するドナーの同定

1. §640.3で要求されているドナー適格性を調べるために、FDAは次の質問を全ドナーに対して、各ドネーションごとに尋ねることを勧告する：

「過去12ヶ月間に、あなたは梅毒もしくは淋病に罹患したかもしくはそのための治療を受けたことがありますか?」(脚注2)

血液採取・取扱施設が短縮タイプのドナー病歴アンケートを頻回、反復ドナーに行っている場合には、FDAはその施設がそれらのドナーに対して、最後のドネーション以降に何らかの新たな医療上の問題や診断、および何らかの新しい医学的治療を受けたことがあるか尋ねることを勧告する。

2. FDAは、ドナーが過去12ヶ月間の間に梅毒か淋病に罹患していたことがある、または、梅毒か淋病の治療を受けたことがあると言明した場合には、そのドナーが梅毒か淋病との診断を受けてから12ヶ月間、もしくは治療の完了後12ヶ月間は、血液採取・取扱施設はそのドナーを不適格とすることを勧告する。この12ヶ月間が経過した後は、当該ドナーは、ドナー適格性判断基準の全てを満足する場合には、再度ドネーションする資格を得ることができる。

B. 梅毒の検出に非トレポネーマスクリーニング試験を記録にとどめる試験として用いる場合のドナー試験と管理(図1参照)

血液採取・取扱施設は各血液ドネーションごとに梅毒の血清学的試験を行わなければならない(§610.40(i))。血液採取・取扱施設は原料血漿のドナーについては少なくとも4ヶ月ごとに梅毒の試験を行わなければならない(§640.65(b)(1)(i))。FDAは梅毒についてドネーションをスクリーニングするために用いられる血清学的試験は全て、そのような使用を意図していることについてFDAが承認したものであり、また、その試験キットの添付文書中に記載の使用方法に従って実施することを勧告する。

1. 非トレポネーマスクリーニング試験が非反応性の場合には、当該ドナーは梅毒感染について陰性と見なされる。血液採取・取扱施設はそのドネーションが梅毒関連以外の全ての基準に合致している限りはそのドネーションを出荷することができ、また当該ドナー

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を適格者として保持しておくことができる。(トレポネーマスクリーニング試験で繰り返し反応性を示したために、以前に不適格とされたドナー(第 IV.C.3.b.節の勧告事項を参照せよ)、または当該時点よりも早期のドネーションの時点で、追加で行われたトレポネーマ試験が陽性であったドナー(第 IV.B.3.b.説を参照せよ)については、再登録(再適格化)の判断基準があることに留意せよ)。

2. 非トレポネーマスクリーニング試験で繰り返し反応性を示した場合には、血液採取・取扱施設は当該ドナーを無期限に不適格としなければならず(§610.41(a))、また、血液採取・取扱施設は当該ドネーションを、出荷もしくは使用の例外規定が適用される場合以外は出荷もしくは使用してはならない(§610.40(h))。しかし、原料血漿ドナーは、注射用以外の製品へとさらに製造するために血漿をドネーションすることは可能である(§640.65(b)(2)(ii))。§610.40(h)(2)の例外が適用されない場合には、血液および血液成分のドネーションは、下記に示す方法を用いてトレポネーマ試験で陰性の結果が得られない限りは、そのドネーションを用いてはならない(§610.40(h))。当該ドナーは下記に示す方法に従えば再適格化の資格を得ることができる。

製品の管理と不適格とされたドナーの§610.41(b)のもとでの再適格化

3. 非トレポネーマ試験が繰り返し反応性であった場合には、血液採取・取扱施設は、問題となったドネーションから得られたサンプル、もしくは後日当該ドナーから採取したフォローアップサンプルのいずれかを用いて、トレポネーマ試験(脚注 3)を行うことができる。
   a. 上記のトレポネーマ試験結果が陰性であった場合(それは反応性を示した非トレポネーマ試験結果が生物学的には偽陽性の結果であったことを示唆するものであるが)、血液採取・取扱施設は当該ドナーを§610.41(b)のもとに再適格化することができる。当該サンプルが、問題となったドネーションからのものであった場合には、当該ドネーションが他の全ての判断基準に合致したものであれば、当該ドネーションを出荷することができるが(§610.40(h)(2)(vi))、その場合の表示は§610.40(h)(2)(vi)および§606.121 に従って適切に行われなければならない。血液採取・取扱施設は生物学的に偽陽性であったスクリーニング試験結果の医学的意義についてドナーカウンセリングを考慮することができる。
   b. トレポネーマ試験結果が陽性であった場合には、血液採取・取扱施設は当該ドナーを無期限に不適格とし続けなければならず(§610.41(a))、出荷もしくは使用についての例外規定が適用される場合(§610.40(h))を除いては、当該ドネーションを廃棄しなければならない。

血液採取・取扱施設は当該ドナーが次のような場合には、§610.41(b)のもとで当該ドナーを再適格化することができる:
   i. 次回ドネーションの少なくとも 12 ヶ月前の時点で、梅毒の治療が成功を収めて完了したとの医師もしくは公衆衛生クリニックからの書面による確証があること、および
   ii. 梅毒以外のドナー適格性判断基準の全てに合致していること。

§610.41(b)のもとで許容しうる再適格化のアルゴリズムには、再適格化されたドナーの次回ドネーションおよびその後のドネーションを非トレポネーマスクリーニング試験を用いて行うことが含まれていなければならない。その非トレポネーマ試験は、抗生物質療法に対する患者の応答をモニターする際に有用である。

C. 梅毒の検出にトレポネーマスクリーニング試験を記録にとどめる試験として用いる場合のドナーの試験と管理(図 1 を参照せよ)
血液採取・取扱施設は各血液ドネーションごとに梅毒の血清学的試験を行わなければならない(§610.40(i))。血液採取・取扱施設は原料血漿のドナーについては少なくとも 4 ヶ月ごとに梅毒の試験を行わなければならない(§640.65(b)(1)(i))。FDA は梅毒についてドネーションをスクリーニングするために用いられる血清学的試験は全て、そのような使用を意図していることについて FDA が承認したものであり、また、その試験キットの添付文書中に記載の使用方法に従って実施することを勧告する。
1. トレポネーマスクリーニング試験が非反応性の場合には、当該ドナーは梅毒感染について陰性と見なされる。血液採取・取扱施設はそのドネーションが梅毒関連以外の全ての基準に合致している限りはそのドネーションを出荷することができる。

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2. トレポネーマスクリーニング試験で繰り返し反応性を示した場合には、血液採取・取扱施設は当該ドナーを無期限に不適格としなければならず、また、血液採取・取扱施設は当該ドネーションを、出荷もしくは使用の例外規定が適用される場合以外は出荷もしくは使用してはならない(§610.40(h))。しかし、原料血漿ドナーは、注射用以外の製品を製造するための血漿をドネーションすることは可能である(§640.65(b)(2)(iv))。当該ドナーは下記に示す方法に従えば再適格化の資格を得ることができる。

不適格とされたドナーの§610.41(b)のもとでの再適格化

3. トレポネーマ試験が分析対象物とは関連しない理由によって偽陽性となる可能性があるので(例えば、試験の実施の間に過剰なコンジュゲートの除去を行わなかった、など)、当該ドナーは再適格化の資格がある。血液採取・取扱施設は、記録にとどめるための試験として用いた、当初のトレポネーマスクリーニング試験とは異なるもう1つのトレポネーマスクリーニング試験を、問題となったドネーションから得られたサンプル、もしくは後日当該ドナーから採取したフォローアップサンプルのいずれかを用いて、行うことができる(脚注4)。

a. 追加で行ったトレポネーマスクリーニング試験結果が陰性であった場合には、血液採取・取扱施設は当該ドナーを再適格化することができる。
b. 追加で行ったトレポネーマスクリーニング試験結果が陽性であった場合には、当該ドナーは無期限に不適格なままとする(§610.41(a))。当該ドナーは、すぐ下に記載のように、再適格化の資格を得ることができる。

血液採取・取扱施設は追加で行ったトレポネーマスクリーニング試験で陽性であった当該ドナーから得たサンプルを、非トレポネーマスクリーニング試験を用いて試験することができる。

i)当該の非トレポネーマスクリーニング試験結果が非反応性であった場合は、血液採取・取扱施設は当該ドナーが次のような場合には§610.41(b)のもとに再適格とすることができる：
A) 次回ドネーションの少なくとも2ヶ月前の時点で、梅毒の治療が成功を収めて完了したとの医師もしくは公衆衛生クリニックからの書面による確証があること(脚注5)、および
B) 梅毒以外のドナー適格性判断基準の全てに合致していること。

§610.41(b)のもとで許容しうる再適格化のアルゴリズムには、再適格化されたドナーの次回ドネーションおよびその後のドネーションを非トレポネーマスクリーニング試験を用いて行うことが含まれていなければならない。

ii)当該の非トレポネーマスクリーニング試験結果が繰り返し反応性であった場合には、当該ドナーは無期限に不適格としたままとする(§610.41(a))。血液採取・取扱施設は、当該ドナーがその後、次のようである場合には、再適格化させることができる(§610.41(b))：
A) 次回ドネーションの少なくとも12ヶ月前の時点で、梅毒の治療が成功を収めて完了したとの医師もしくは公衆衛生クリニックからの書面による確証があること、および
B) 梅毒以外のドナー適格性判断基準の全てに合致していること。

§610.41(b)のもとで許容しうる再適格化のアルゴリズムには、再適格化されたドナーの次回ドネーションおよびその後のドネーションを非トレポネーマスクリーニング試験を用いて行うことが含まれていなければならない。

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報告企業の意見	今後の対応	
梅毒トレポネーマ（Treponema pallidum）はスピロヘータ科トレポネーマ属の一種で、大きさは0.10～0.18×6～20μm（平均0.13～0.15×10～13μm）のラセン状の細菌で、低温保管や凍結乾燥、加熱処理により死滅するとされている。そのため、万一原料血漿に梅毒トレポネーマが混入したとしても、製造工程において不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、段の措置はとらない。	

JBPO 2013-004

Guidance for Industry

Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or email at ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Guidance for Industry

Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are providing you, blood establishments that collect Whole Blood or blood components, including Source Plasma, with revised recommendations for screening and testing of donors and management of donations based on screening tests for syphilis.

This draft guidance replaces FDA's draft guidance entitled, "Guidance for Industry: Revised Recommendations for Donor and Product Management Based on Screening Tests for Syphilis," dated June 2003 (Ref. 1), and when finalized, will supersede the memorandum of December 12, 1991, entitled "Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing" (Ref. 2).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Transfusion-Transmission of Syphilis

Syphilis, caused by the spirochete *Treponema pallidum (T. pallidum)*, is most often acquired after sexual contact with an infected individual. Syphilis can also be transmitted from mother to child or, rarely, transmitted by transfusion of blood or blood components from donors with active syphilis (Ref. 3). The last reported case of transfusion-transmitted syphilis in the United States (U.S.) occurred in 1966 (Ref. 4). Universal

testing of blood donors may have played a role in the disappearance of transfusion-transmitted syphilis. Other possible explanations for the decline in transfusion-transmitted syphilis include: that direct donor-to-recipient transfusions no longer take place; inactivation of *T. pallidum* (a cold-sensitive microorganism) in refrigerated blood components; the decline in rates of syphilis in the general population, which in turn is reflected in the donor population; self-deferral of blood donors who are ill during spirochetemia (presence of spirochetes—the causative agent of syphilis infection—in the circulating blood); deferral of potential donors who demonstrate high risk behavior for acquiring syphilis infection (e.g., persons who received money, drugs, or other payment for sex) through donor eligibility screening processes; wide use of antibiotics among transfusion recipients; and difficulties in diagnosing transfusion-transmitted syphilis in recipients (Ref. 5). However, none of these explanations has been quantified or adequately validated.

Current testing requirements for *T. pallidum* are included in Title 21 Code of Federal Regulation (CFR) Part 610, Subpart E (Testing Requirements for Communicable Disease Agents), specifically under § 610.40(i) (21 CFR 610.40(i) and in § 640.65 (21 CFR 640.65) for Source Plasma donors. FDA has sought public comments on the continued need for syphilis testing on several occasions, most recently in a proposed rule entitled "Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use," dated November 8, 2007 (72 FR 63416). FDA is now reviewing comments to the proposed rule. Current requirements to test blood donations for syphilis (§ 610.40(i)) as well as Source Plasma donors (§ 640.65) remain in effect.

Information from the American Red Cross serological testing of donors revealed that there were 324 cases of syphilis infections among American Red Cross repeat allogeneic donors in 2007-2008, a figure several times higher than the numbers of repeat allogeneic donors identified with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-cell lymphotropic virus (HTLV) infections, which were 92, 47, 127 and 9, respectively, during the same time period (Ref. 6). Several published studies (Refs. 7 through 12) reporting the presence or absence of *T. pallidum* nucleic acid in blood samples from individuals with confirmed or possible syphilis detected spirochete nucleic acid in blood samples from persons with syphilis, some of whom had a latent infection with no symptoms. This suggests that some asymptomatic blood donors might have spirochetemia. Donations from such blood donors may have the potential to transmit syphilis to recipients.

B. Testing of Blood and Blood Components for Syphilis

Under § 610.40(i), you must perform a serological screening test for syphilis on each donation of blood.[1] Donors who test repeatedly reactive with a screening test for syphilis must be deferred (§ 610.41(a)) and notified of their deferral (21 CFR 630.6). FDA does not require further testing of the donor to confirm infection for syphilis. In accordance

[1] FDA's other regulatory requirements related to syphilis are found under 21 CFR 606.121, 610.41, 640.5(a), 640.14, 640.23(a), 640.33(a), 640.53(a), 640.65(b)(1) and (b)(2), and 640.67.

with § 610.41(b), you may perform additional testing to requalify the donor as described below in sections IV.B and C. In accordance with § 610.40(h)(2)(vi), FDA allows use of blood and blood components, excluding Source Plasma, that test reactive by a screening test for syphilis, if the donation is further tested by an adequate and appropriate test which demonstrates that the reactive screening test is a biological false-positive, and the blood or blood component is labeled with both test results.

FDA requirements regarding syphilis testing specific to Source Plasma are as follows:

1. Current collection, testing and labeling requirements related to results of serologic tests are found in §§ 640.65, 640.67, and 606.121.
2. Note that FDA regulations require that a sample of blood be drawn from Source Plasma donors on the day of the first medical examination or plasmapheresis, whichever comes first, and at least every 4 months thereafter, and that these samples must be tested for syphilis (§ 640.65(b)(1)(i)).
3. FDA regulations also require that a donor with a reactive test result for syphilis must not be plasmapheresed again until the donor tests nonreactive, except as stated in points 4 and 5, below (§ 640.65(b)(2)(ii)).
4. The regulations permit a donor with a reactive biologic false-positive syphilis test result to be plasmapheresed, provided that the donor's file: (a) identifies the reactive serologic test and the results used to confirm the biologic false-positive results; and (b) indicates that the physician on the premises has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participating in the plasmapheresis program (§ 640.65(b)(2)(iii)).
5. The regulations also permit a donor with a reactive syphilis test result to be plasmapheresed to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis, provided that: (a) the physician on the premises approves the donation; and (b) the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has commenced and that continuance in the plasmapheresis program will not interfere with or jeopardize the syphilitic donor's treatment (§ 640.65(b)(2)(iv)).
6. Plasma collected from a donor with a reactive test result for syphilis must be appropriately labeled, as stated in § 606.121(e)(5)(iv).

III. CHARACTERISTICS OF SEROLOGIC ASSAYS FOR SYPHILIS

There are two different types of serologic assays for syphilis: (A) nontreponemal assays; and (B) treponemal assays.

(A) ***Nontreponemal assays***, such as the rapid plasma reagin (RPR) test, the venereal disease research laboratory (VDRL) test, and the automated reagin test (ART), are non-specific tests that detect "reagin" antibodies directed against an antigen called cardiolipin

that is present in a variety of tissues. Antibodies to cardiolipin appear in the serum of persons with active syphilis and with some other conditions. However, note that some individuals who were previously infected with syphilis but were successfully treated maintain low levels of antibody to cardiolipin for a long time; such persons are classified as being "serofast."

Sera and plasma from individuals previously infected with syphilis who were successfully treated do not generally remain reactive in nontreponemal tests for more than one to two years after successful treatment. Therefore, persons with active or recently treated syphilis infections generally have reactive results in nontreponemal tests, while uninfected persons or persons successfully treated years earlier usually have nonreactive nontreponemal test results, but retain specific antibody reactivity.

Nontreponemal assays are useful in identifying recent syphilis infection, and to monitor the progression of syphilis and response to antibiotic therapy. Retesting sera that are reactive in nontreponemal assays using a specific treponemal test may be of value in distinguishing true-positive results that indicate active syphilis infection from biological false-positive results due to other conditions.

(B) ***Treponemal assays*** include chemiluminescence immunoassays, enzyme immunoassays (EIA), fluorescent treponemal antibody "absorbed" assays (FTA-ABS), *Treponema pallidum* microhemagglutination assays (MHA-TPA) and *Treponema pallidum* particle agglutination assays (TP-PA). Treponemal assays test for antibodies to antigens that are specific to treponemes. Although treponemal assays are useful in identifying recent and historically remote syphilis infections, they are not useful in monitoring the progression of syphilis or response to antibiotic therapy. With some exceptions, positive results of tests for specific treponemal antibodies remain positive throughout an individual's life regardless of whether the individual is currently infected or has been cured following successful treatment (Ref. 13).

Since both the nontreponemal and treponemal assays detect antibodies rather than the infectious treponemes themselves, neither assay reliably identifies patients in the "window period" of very early syphilis, after infection has been acquired but before antibodies to either treponemal antigens or to cardiolipin have appeared.

Prior to 1990, blood establishments typically used nontreponemal tests to screen donors for syphilis and then performed a treponemal test on the reactive samples to determine the specificity of nontreponemal test results. In 1990, the Center for Biologics Evaluation and Research cleared a 510(k) pre-market notification for an automated modified microhemagglutination test that detects specific antibodies to *T. pallidum*. After this new treponemal assay was implemented for screening donors, some repeat blood donors who had formerly been found suitable based on nonreactive nontreponemal test results were deferred because they were found to have specific antibodies to *T. pallidum*. This test eliminated most biological false-positive nontreponemal screening test results, and its use caused no overall increase in the total number of donors deferred (Refs. 14 and 15). Many blood establishments

now use automated treponemal assays with high throughput that have been cleared by FDA for purposes of screening donors for syphilis, such as the treponemal assays chemiluminescence immunoassays, EIA, and TP-PA. Some blood establishments, however, continue to use RPR, a nontreponemal assay, as a screening assay. Therefore, we are providing recommendations for management of donors and blood and blood components for situations in which a blood establishment would use either a nontreponemal screening test or a treponemal screening test.

To distinguish the results of screening tests for syphilis from the results of additional syphilis tests, we use the terms "reactive" and "nonreactive" for results of screening tests (both nontreponemal and treponemal) and reserve the terms "positive" and "negative" for results of subsequent treponemal tests (used for donor requalification) on samples of the same blood specimen previously used for screening. A test result that is read as "indeterminate", "questionable", or "equivocal" according to the package insert should be considered as equivalent to a reactive or positive test result for purposes of this document.

Establishments that screen donors using a nontreponemal assay as the test of record may also use a treponemal diagnostic test for the purposes of donor counseling or consideration of requalification after deferral, and also for demonstrating that the reactive screening test is a biological false positive (§ 610.40(h)(2)(vi)). However, we are recommending that in all other instances, serologic tests used to screen donors for syphilis should be cleared by FDA for such intended use (see recommendations in sections IV.B and C.)

IV. RECOMMENDATIONS FOR DONOR TESTING AND MANAGEMENT AND PRODUCT DISPOSITION WHEN USING TESTS FOR SYPHILIS

A. Identification of Donors with a History of Syphilis

1. To assess the suitability of the donor as required in § 640.3, we recommend that you ask the following question of all donors at each donation:

   "In the past twelve months have you had or been treated for syphilis or gonorrhea?"[2]

   If you are administering an abbreviated donor history questionnaire to frequent, repeat donors, we recommend that you ask these donors if they have had any new medical problems or diagnoses and any new medical treatments since their last donation.

2. We recommend that you defer donors who state that in the past 12 months they have had or have been treated for syphilis or gonorrhea for 12 months after being told they had syphilis or gonorrhea or after completion of

[2] This question is currently included in the AABB Full-Length Donor History Questionnaire (DHQ), Version 1.3, dated May 2008, and DHQ Version 1.1, dated June 2005, that have been found acceptable by FDA in guidance.

treatment. After this 12-month period, the donor may be eligible to donate again, provided that the donor satisfies all applicable donor eligibility criteria.

B. Donor Testing and Management When Using a Nontreponemal Screening Test as the Test of Record for the Detection of Syphilis (See Figure 1)

You must perform a serological test for syphilis on each donation of blood (§ 610.40(i)). You must test a donor of Source Plasma for syphilis at least every 4 months (§ 640.65(b)(1)(i)). We recommend that all serological tests used to screen donations for syphilis be cleared by FDA for such intended use and that you follow the instructions for use in the package insert.

1. If the nontreponemal screening test is nonreactive, the donor is considered to be negative for syphilis infection. You may release the donation, provided it meets all other requirements, and retain the donor. (Note that there are reentry criteria available for a donor previously deferred because of a repeatedly reactive treponemal screening test (see recommendation in section IV.C.3.b.) or who had a positive additional treponemal test at the time of an earlier donation (see recommendation in section IV.B.3.b.)).
2. If the nontreponemal screening test is repeatedly reactive, you must defer the donor indefinitely (§ 610.41(a)) and you must not ship or use the donation, unless an exception for shipment or use is applicable (§ 610.40(h)). However, Source Plasma donors may be allowed to donate plasma for further manufacture into noninjectable products (§ 640.65(b)(2)(ii) through (iv)). Absent an exception under § 610.40(h)(2) being applicable, donations of blood and blood components must not be used (§ 610.40(h)) unless a negative treponemal test result is obtained using the method described below. The donor may be eligible for reentry following the method described below.

Product Management and Reentry Under § 610.41(b) of Deferred Donors

3. If the nontreponemal test is repeatedly reactive you may perform a treponemal test[3] using either a sample from the index donation or a follow-up sample from the donor collected at a later date.

    a. If the treponemal test result is negative (suggesting that the reactive nontreponemal test result was a biological false-positive result), you may reenter the donor under § 610.41(b). If the sample tested was from the index donation, the donation may be released (§ 610.40(h)(2)(vi)) provided the donation meets all other criteria, but must be appropriately

[3]Establishments may use a treponemal diagnostic test for the purposes of donor counseling or consideration of requalification after deferral, and also for demonstrating that the reactive screening test is a biological false-positive (§ 610.40(h)(2)(vi)).

labeled under §§ 610.40(h)(2)(vi) and 606.121. You may consider counseling the donor about the potential medical significance of a biological false-positive screening test.

b. If the treponemal test result is positive, you must continue to defer the donor indefinitely (§ 610.41(a)) and discard the donation unless an exception for shipment or use is applicable (§ 610.40(h)).

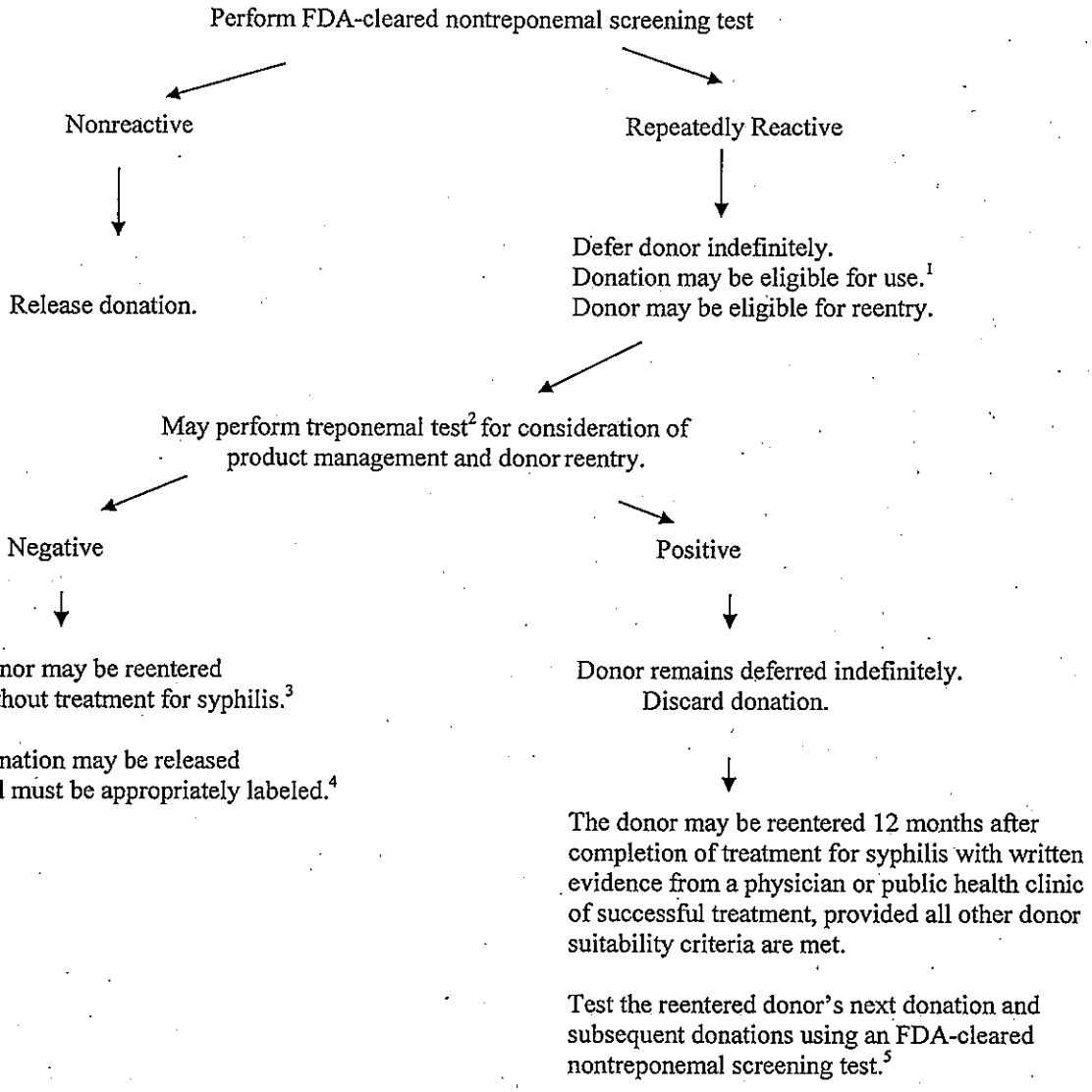
   You may reenter the donor under § 610.41(b) if the donor subsequently:

   i. Presents written evidence from a physician or public health clinic of successful treatment of syphilis that was completed at least 12 months prior to the next donation; and

   ii. Meets all other donor eligibility criteria.

An acceptable reentry algorithm under § 610.41 (b) must include the use of a nontreponemal screening test to test the reentered donor's next donation and subsequent donations. The nontreponemal screening test is useful in monitoring a patient's response to antibiotic therapy.

Figure 1: Donor Testing and Management When Using a Nontreponemal Screening Test as the Test of Record for the Detection of Syphilis



[1]Source Plasma donations with these test results may be used under some circumstances, but the donor is deferred unless certain conditions apply (§§ 610.40(h)(2)(vii) and 640.65(b)(2)(ii) through (iv)). Absent the applicability of an exception under § 610.40(h)(2), donations of blood and blood components must not be used unless a negative treponemal test result is obtained (§ 610.40(h)).

[2] You may use a treponemal diagnostic test for the purposes of donor counseling or consideration of requalification after deferral, and also for demonstrating that the reactive screening test is a biological false-positive (§ 610.40(h)(2)(vi).

[3]Consider counseling the donor about the potential medical significance of a biological false-positive screening test.

[4]Sample tested must be from index donation. You must label such donations as reactive by a screening test for syphilis and negative by a treponemal test (§ 610.40(h)(2)(vi)).

[5]An acceptable reentry algorithm under § 610.41(b) must include the use of a nontreponemal screening test to test the reentered donor's next donation and subsequent donations.

C. Donor Testing and Management When Using a Treponemal Screening Test as the Test of Record for the Detection of Syphilis (See Figure 2)

You must perform a serological test for syphilis on each donation of blood (§ 610.40(i)). You must test a donor of Source Plasma for syphilis at least every 4 months (§ 640.65(b)(1)(i)). We recommend that all serological tests used to screen donations for syphilis be cleared by FDA for such intended use and that you follow the instructions for use in the package insert.

1. If the treponemal screening test is nonreactive, the donor is considered to be negative for syphilis infection. You may release the donation, provided it meets all other requirements.

2. If the treponemal screening test is repeatedly reactive, you must defer the donor indefinitely and you must not ship or use the donation, unless an exception for shipment or use is applicable (§ 610.40(h)). However, Source Plasma donors may be allowed to donate plasma for manufacture into non-injectable products (§ 640.65(b)(2)(iv)). The donor may be eligible for reentry following the method described below.

Reentry Under § 610.41(b) of Deferred Donors

3. Because the possibility exists that a treponemal test might be false-positive for reasons unrelated to the analyte (e.g., failure to remove excess conjugate during the performance of the test), the donor may be eligible for reentry. You may perform another treponemal screening test that is different from the initial treponemal screening test used as the test of record, using either a sample from the index donation or a follow-up sample from the donor collected at a later date.[4]

   a. If the additional treponemal screening test result is negative, you may reenter the donor.

   b. If the additional treponemal screening test result is positive, the donor remains deferred indefinitely (§ 610.41(a)). The donor may be eligible for reentry, as described immediately below.

      You may test the sample from the donor which was positive on the additional treponemal screening test using a nontreponemal screening test.

[4] When treponemal screening test results are repeatedly reactive, we do not consider negative results on an additional treponemal test to be indicative of biological false-positives on the screening test under § 610.40(h)(2)(vi). Regardless of the result from the additional treponemal screening test result, under § 610.40(h) you must not release the index donation unless an exception applies. Source Plasma donations with these test results may be used under some circumstances, provided that the requirements under §§ 610.40(h)(2)(vii) and 640.65(b)(2)(ii) through (iv) are met.

i) If the nontreponemal screening test result is nonreactive, you may reenter the donor under § 610.41(b) if the donor:
   A) Presents written evidence from a physician or public health clinic of successful treatment for syphilis completed at least 2 months before the next donation[5]; and
   B) Meets all other donor eligibility criteria.

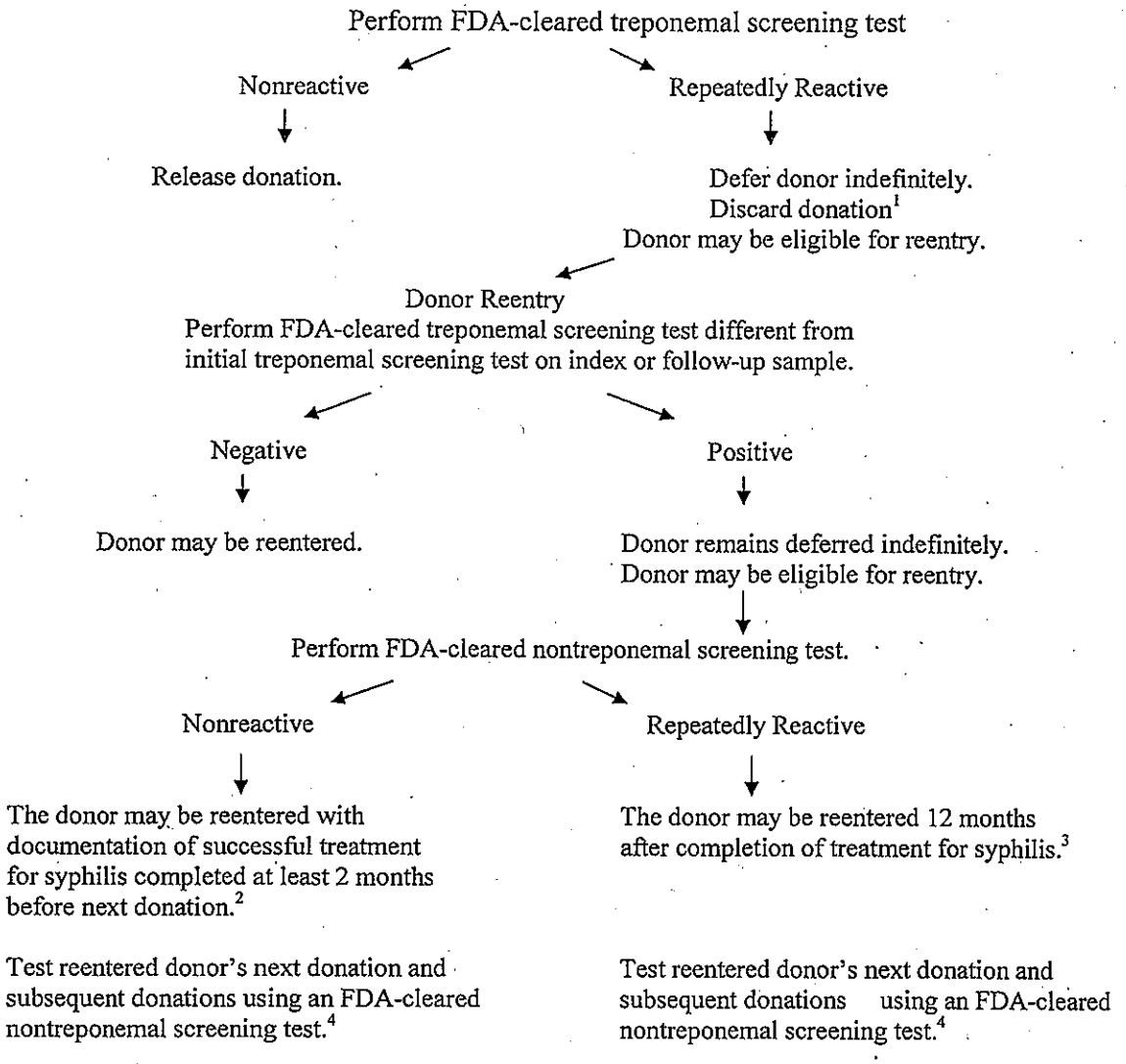
   An acceptable reentry algorithm under § 610.41(b) must include the use of a nontreponemal screening test to test the reentered donor's next donation and subsequent donations.

ii) If the nontreponemal screening test result is repeatedly reactive, the donor remains deferred indefinitely (§ 610.41(a)). You may reenter the donor (§ 610.41(b)) if the donor subsequently:
   A) Presents written evidence of successful treatment for syphilis that was completed at least 12 months prior to the next donation; and
   B) Meets all other donor eligibility criteria.

   An acceptable reentry algorithm under § 610.41(b) must include the use of a nontreponemal screening test to test the reentered donor's next donation and subsequent donations.

[5] We recommend that successful treatment should have been completed at least 2 months before the next donation to allow sufficient time for persistent active syphilis because of inadequate treatment or treatment failure to become manifest, as evidenced by appearance of a reactive nontreponemal screening test result (Ref. 16).

Figure 2: Donor Testing and Management When Using a Treponemal Screening Test as the Test of Record for the Detection of Syphilis



[1]Source Plasma donations with reactive test results for syphilis may be used under some circumstances, but the donor is deferred, unless certain conditions apply (§§ 610.40(h)(2)(vii) and 640.65(b)(2)(ii) through (iv)). Donations of blood and blood components must be discarded, unless an exception is applicable ((§ 610.40(h)(2)). Note that all applicable labeling requirements must be met, should you be able to use the donations (§§ 606.121 and 610.40(h)(2)).

[2]The donor may be reentered 2 months after completion of treatment with a signed written statement from a physician or public health clinic of successful treatment, provided all other donor suitability criteria are met.

[3]The donor may be reentered 12 months after completion of treatment with a signed written statement from a physician or public health clinic of successful treatment, provided all other donor suitability criteria are met.

[4]An acceptable reentry algorithm under § 610.41(b) must include the use of a nontreponemal screening test to test the reentered donor's next donation and subsequent donations.

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医薬品
医薬部外品　　研究報告　調査報告書
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識別番号・報告回数			報告日	第一報入手日 2013年03月04日	新医薬品等の区分 該当なし	厚生労働省処理欄

一般的名称	乾燥濃縮人アンチトロンビンIII	研究報告の公表状況	fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/2013/02/26	公表国 アメリカ
販売名 （企業名）	①ノイアート静注用500単位　（日本血液製剤機構） ②ノイアート静注用1500単位　（日本血液製剤機構）			

研究報告の概要

業界向けガイダンス
原料血漿ドナーのクリーニングに用いる許可予定のドナー病歴問診票（完全版及び簡略版）並びに付属資料の導入について

Ⅰ．はじめに

本ガイダンスでは、血漿たん白質製剤協会（PPTA）が作成したドナーの病歴問診票（標準化した完全版及び簡略版）並びにその付属資料（2012年9月付、バージョン1.2）を、原料血漿ドナーの病歴情報の収集に関する米国食品医薬品局（FDA）の要件及び勧告に則っており、許可し得るものと認める。今後、我々FDAは、許可し得るものとして、他の原料血漿ドナー病歴問診票並びに付属資料を認める可能性がある。FDAは、原料血漿ドナー病歴問診票並びに付属資料（以下、「SPDHQ文書」とする）の現在の認められたバージョンを、FDAウェブサイト上に公開するつもりである。

SPDHQ文書は、原料血漿を採取する血液事業者（以下、「製造業者」とする）に対し、原料血漿ドナー（以下、「ドナー」とする）の供血適合性を判断するために問診を行う際の具体的な手順を提供するものである。FDAは、本手引書中の「適格性（eligibility）」という用語は、連邦規則集第21章640.63（21 CFR 640.63）に記載されているドナー適格者の要件を指している。許可予定のSPDHQ文書は、21 CFR 640.63中で規定されているドナー適格者の要件に合致するかどうかの判断材料となる病歴情報を原料血漿ドナーから得るための一手段を原料血漿製造業者に提供し得るものであるとFDAが判断したものである。

また、本手引書は、許可予定のSPDHQ文書を実施することを選択した原料血漿製造業者に対し、SPDHQの履行による製造変更の報告を行う際の21 CFR 601.12（§ 601.12）に準拠した報告方法に関する勧告を行うものである。本手引書を含むFDAの手引書/文書は、法的強制力のある責務を設定したものではない。その代わりに、これらの手引書は話題に関するFDAの現在の見解を説明しており、特に規制上や法令上の要件が引用されていない限り、勧告としてのみ理解されるべきものである。FDAの手引書における「～すべきである（should）」という語は、提案、或いは勧告を示すものであり、必要条件を意味するものではない。

Ⅱ．背　　景

21 CFR 640.63（a）は、採血日に原料血漿ドナーの適格性を判断する旨の要件が規定されている。（「採血日」については、ドナー病歴問診票へのドナーの回答が明確であることが確認されるか、或いは採血から24時間以内に記載漏れ事項への回答を得たことが確認された時点と解釈する）。この様な適格性の判断は、ドナーが良好な健康状態にあることを保証し、血液及び血液成分を介して伝播し得る感染症を予防することを目的とするものである（21 CFR 640.63(a-d)）。血液及び血液成分のドナーの供血適格性の判断は、身体的評価、並びに病歴及び感染症の危険因子に関する質問に対するドナーの回答に基づいて行われる。適切な臨床検査法がないか、若しくは検査による検出が不可能な感染初期の段階、或いはウインドウピリオドにある疾患及び健康状態のリスクの判断においては、ドナーに対する問診スクリーニングが特に重要になる。

ドナーのスクリーニングを目的とする正式な統一問診票が最初に導入されたのは、約60年前であった。ドナーへの問診票は不適格なドナーを排除する上で有用であるが、スクリーニング過程で情報が正しく理解されないか、或いは把握しきれない場合があるために、誤った判定が下されることがあった。ドナースクリーニングに関しては、この問題を検討するために開かれたFDA主催のワークショップで指摘さ

使用上の注意記載状況・その他参考事項等

2．重要な基本的注意
(1)本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-1抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohnの低温エタノール分画で得た画分から人アンチトロンビンIIIを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

文献番号 16

れたように、問診票に関する様々の要因（質問の複雑さ、ドナーの記憶力、ドナーの健康及び安全、回答に対するドナーの満足度及び意欲など）、投与前に実施すべき血液製剤の検査、並びに血液及び血液成分の最終消費/レシピエントに対するリスクを考慮すべきである。問診票は冗長で、時間がかかると考えるドナーもおり、ドナーの理解と満足度を上げる方法として、特に頻回ドナーに対しては、コンピューターを使用した自己入力式の簡略版の問診票を使用する等の方策が提案されている。FDA は、2003 年 7 月付で「業界向け手引書：ドナー問診過程の効率化：質問票の自己管理についての勧告」、「ドナー問診の効率化に関する手引書」と題した手引書を発行しており、その中で血液事業者及び血漿事業者が特定のドナーに対し自己記入式の問診票を使用することにより、ドナースクリーニングのプロセスを簡略化する方法について解説している。

完全版及び簡略版問診票は一緒に導入されるようになっている。例えば、血液事業者が簡略版 PPTA ドナー病歴問診票の導入を選んだ場合、使用の手引き中に記載されている通り、血液事業者は完全版 PPTA ドナー病歴問診票も導入すべきである。問診票の完全版及び簡略版ともに、原料血漿事業者の担当者が管理するか、或いは事業者の担当者のフォローアップのもと、ドナーによる自己管理ができるように作成されている。

SPDHQ 文書は以下の資料が含まれており、第IV節 A.2 に書かれているものを除いて、これらを完全に用いる予定である。

- 完全版ドナー病歴問診票
  - o 問診票Ⅰ－HIV-1 グループ O の変異株を検出する公認検査法を実施している原料血漿事業者用
  - o 問診票Ⅱ－HIV-1 グループ O の変異株を検出する公認検査法を実施していない原料血漿事業者用
- PPTA 完全版ドナー病歴問診票使用の手引き－用語解説、フローチャート及び参考文献が含まれ、問診の実施方法の記述、「補足質問」への可能なドナー回答を十分に評価するための関連質問を含む。
- 簡略版ドナー病歴問診票－頻回原料血漿ドナー用
- PPTA 簡略版ドナー病歴問診票使用の手引き－用語解説、フローチャート及び参考文献が含まれ、該当ドナー及び問診の実施方法の記述、「補足質問」への可能なドナー回答を十分に評価するための関連質問を含む。
- 医薬品リスト－ドナー禁止の基準となる医薬品のリストを含む。
- リスクに関するポスター－ドナー禁止の基準となるリスク及び健康状態についてドナーを教育する。
  - o ポスターⅠ－HIV-1 グループ O の変異株を検出する公認検査法を実施している原料血漿事業者用
  - o ポスターⅡ－HIV-1 グループ O の変異株を検出する公認検査法を実施していない原料血漿事業者用
- 旅行に関するポスター－血液及び血液成分を介して伝播される疾患の流行地域を特定している。
  - o 旅行ポスターⅠ－HIV-1 グループ O の変異株を検出する公認検査法を実施している原料血漿事業者用
  - o 旅行ポスターⅡ－HIV-1 グループ O の変異株を検出する公認検査法を実施していない原料血漿事業者用

Ⅲ. PPTR SPDHQ 文書の許可について

FDA は、原料血漿ドナーのスクリーニングに用いることに関して、SPDHQ 文書（バージョン 1.2）は使用して差し支えないと考える。ただ、これらの文書はドナー適格性に係る問診に関連する FDA の要件及び勧告に合致しているが、以下の例外がある。SPDHQ 文書には、現在 FDA による要件、或いは勧告が提示されていないドナーの病歴（癌；臓器、組織、或いは骨髄の移植；骨、或いは皮膚の移植；妊娠）を問う質問が含まれている。FDA は、当許可予定の SPDHQ 文書の使用を FDA の規制要件を満たすための一手段として認めるが、これによりドナースクリーニング、或いは供血禁止がなされることを要求、或いは勧告するものではない。また、血液事業者が当許可予定の SPDHQ 文書を使用する場合、上記の質問を簡略したとしても、FDA の要件は満たしている。

FDA は、当許可予定の SPDHQ 文書がドナースクリーニングに有効な手段であることは認めるが、血液事業者に対し許可予定の SPDHQ 文書の履行を求めるものではない。血液事業者は、自社で作成した、或いは以前の FDA 公認のドナー病歴問診票（完全版及び簡略版）並びに付属資料を、引き続き使用しても良い。これらの資料は、SPDHQ 文書におけるものと異なる手段及び文言を含んでもよい。今後、血液事業者は 21 CFR 601.12 に準拠し、SPDHQ 文書におけるものと異なる新しい手段及び資料を用いることを良しとする。

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IV. 許可予定のドナー病歴問診票並びに付属資料の使用に係るFDAへの報告

上記に示したように、FDAは完全版及び簡略版の問診票を一緒に使用することを勧告する。例えば、血液事業者が簡略版PPTAドナー病歴問診票の使用を選択した場合、FDAは血液事業者が完全版PPTAドナー病歴問診票も使用することを勧告する。

A. 許可予定のSPDHQ文書の使用

血液事業者が許可予定のSPDHQ文書の使用を開始する場合には、21 CFR 601.12に準拠し、以下の手順に従ってＦＤＡに報告しなければならない。

1. 原料血漿ドナーへの問診の手順として、許可予定のSPDHQ文書に変更を加えることなく、書式全体を利用する場合、製剤の安全性、或いは有効性に関連する同一性、力価、品質、純度、或いは有効性に悪影響を及ぼす可能性はごく限定的であること考えられ、軽微な変更に該当する。血液事業者は、こうした変更については21 CFR 601.12(d)に準拠し、年次報告書に実施日を明記の上、FDAに提出すること。ドナーが自己記入式の許可予定のSPDHQ文書の適用対象となる場合については、セッションIV. B. を参照のこと。
2. 許可予定のSPDHQ文書の書式全体を使用するが、一部に変更を加え(a)血液事業者がより厳格な独自の選択基準を追加する場合、若しくわ(b)ドナー適格性の判断に関してFDAが要件、或いは勧告を提示していない癌；臓器、組織、或いは骨髄の移植；骨、或いは皮膚の移植；及び妊娠に関連する質問を削除する場合、軽微な変更に該当する。このような変更については、21 CFR 601.12(d)に準拠し、年次報告書に実施日、及び追加した基準、或いは問診票から削除した質問を明記の上、FDAに報告すること。
3. 血液事業者は、SPDHQのフローチャートの形式、或いは文言を変更するが、内容はFDAの要求/勧告するドナー血禁止基準に則っている場合、或いはより厳格なドナー禁止基準を採用する場合、軽微な変更に該当する。血液事業者は、このような変更については21 CFR 601.12(d)に準拠し、年次報告書に実施日、並びに許可予定のSPDHQ文書に加えた変更を明記の上、FDAに報告すること。
4. 許可予定のSPDHQ文書の書式全体を使用するが、現行のプロセスに一致するよう文書の一部（フローチャート以外の文書）を改編する場合、許可予定のSPDHQ文書の文言及び内容の順序に変更を加えるものでなければ、軽微な変更に該当する。このような変更については、21 CFR 601.12(d)に準拠し、年次報告書に実施日、並びに許可予定のSPDHQ文書に加えた変更を明記の上、FDAに報告すること。
5. ドナースクリーニングは、血液成分及びスクリーニング手順の安全性にとって重要である、彼らはの安全性や有効性に関連することができるように同一性、力価、品質、純度、または血液および血液成分の効力に悪影響を及ぼすことが相当な可能性を秘めている製品。従って、特にセクションIV. A. 2-4に特に明記した以外の変更を加えた許可予定のSPDHQ文書を使用する場合は、大幅な変更に該当する。血液事業者は、セクションIV.A.2-4に記述した以外の方法で変更を加えた許可予定のSPDHQ文書を使用したい場合は、21 CFR 601.12 (b) に準拠して、事前承認申請追加項目 (PAS) として届け出ること。なお、届出の際には、以下の文書を提出すること：
    a. FDA申請用紙番号356h『ヒト用新薬・生物学的製剤・抗生物質の新薬承認申請書』
    (http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm;より入手可能)
    b. 要望事項及び提出文書の内容を記述したカバーレター
    c. ドナーの問診及び問診票の使用について記述した標準作業手順書 (SOP)
    d. ドナー病歴問診票及びその付属文書。変更箇所を明確にすること。

事前承認申請追加項目の届け出に当たっては、FDAの1999年5月付「業界向け手引書：輸血用、或いは血液製剤製造用ヒト血液及び血液成分の化学成分・製造管理・施設説明書提出及びFDA申請用紙番号356h『ヒト用新薬・生物学的製剤・抗生物質の新薬承認申請書』」を参照のこと。

B. 自己記入式の許可予定のSPDHQ文書の使用

2003年7月、FDAは「ドナー問診の効率化に関する手引書」を発行し、許可を受けた血液事業者に対し、ドナー病歴問診票の自己記入の手順を、21 CFR 601.12(c)に規定された30日後変更実施追加項目 (CBE30) としてFDAに届け出る旨の勧告を行ったところである。

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この方法を運用するにあたっての管理が充分に行われていることを保証にするには、CBE30 が適切な追加項目であったと判断したためである。しかし、許可予定の SPDHQ 文書に、SPDHQ 使用の手引きにあるような自己記入プロセスの管理に関する指示が含まれている場合は、下記セクションⅣ. B. 1 及びⅣ. B. 2 に記載の通り、年次報告書への記載により報告するか、或いは場合により CBE30 として届け出ても良いと判断したものである。これらの勧告は、「ドナー問診の効率化に関する手引書」における規定を修正するものであり、許可予定の SPDHQ 文書以外の自己記入式の問診票の使用を計画している許可製造業者は、引き続き「ドナー問診の効率化に関する手引書」を参考にするべきである。

許可製造業者が自己記入式の許可予定の SPDHQ 文書を使用する場合は、21 CFR 601.12 に準拠し、以下の手順に従って FDA に報告しなくてはならない：

1. 手書き、或いは視聴覚機器を用いての、許可予定の SPDHQ 文書に記載の自己記入式を選択採用する場合は、軽微な変更に該当する。このような変更については、21 CFR 601.12 に準拠し、年次報告書に実施日を明記の上、FDA に報告すること。
2. コンピューターを用いての双方向型の問診手段を選択する場合は、この変更を追加項目－21 CFR 601.12(c)に規定された 30 日後変更実施（CBE30）－として FDA に報告すること。この場合、如何なる条件下でも全ての回答者が提出される質問及び情報を容易に理解できるとは限らないため、この変更が血液及び血液成分製剤の同一性、力価、品質、純度、或いは有効性に悪影響を及ぼす危険性は中程度である。その上、コンピューターを使用した双方向型の問診手段を初めて実施する際には、電子記録の管理等の新たな問題が生じる可能性がある。従って、FDA は現時点では、コンピューターを使用した双方向型の問診手段の実施を、軽微な変更と認めることはできない。

上記以外の自己記入式の問診票の使用の実施及び報告、及びコンピューターを使用した双方向型の問診手段に係る追加項目の届け出にあたっては、「ドナー問診の効率化に関する手引書」を参照すること。

Ⅴ. 今後の許可予定の SPDHQ 文書の承認及び使用

今後、ドナーの安全、或いは原料血漿の安全性、純度及び有効性に影響を及ぼす可能性のある新たな感染症、内科的疾患、生活行動、地理的暴露、或いは医薬品が現れた場合には、ドナー禁止に関する規制、或いは手引書を発行する可能性がある。新たな対策の実施に伴い、血液事業者のドナー問診に係る SOP の変更、及び許可された SPDHQ 文書の修正が必要となることも考えられる（通常は、問診票の末尾の追加質問用スペースへの質問事項の追加による、或いは新規または改訂版の SPDHQ 文書の実施による）。血液事業者が許可予定の SPDHQ 文書を使用しない場合は、独自の問診票に修正を加えることが必要となる。FDA が新たなドナー禁止基準に関する勧告を行う場合は、同手順書の中に、手順の変更に伴う製造変更の実施及び FDA への報告に関する勧告を盛り込むこととする。改訂版の SPDHQ 文書が利用可能となり、またその文書が許可し得ると考えられる場合は、供血禁止に関する手引書の中で、当該 SPDHQ 文書を許可する予定である。その際は、全ての許可予定の SPDHQ 文書を、FDA のウェブサイト上で公開することにする。

全ての事業者の施設において、新たなドナー病歴問診票の使用に備えた準備を整えておくことを勧告する。

Ⅵ. 問い合わせ先

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報告企業の意見	今後の対応	
血液媒介ウイルス（blood mediated virus）は、B型肝炎ウイルス（HBV）、C型肝炎ウイルス（HCV）、ヒト免疫不全ウイルス（HIV）、サイトメガロウイルス（CMV）、成人T細胞白血病ウイルス（HTLV-1）、パルボウイルスB19（B19）などの血液を媒介して感染を起こし得る病原体ウイルスである。本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-1抗陰性で、かつALT（GPT）値でスクリーニングを実施している。更に，プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査（NAT）を実施し、適合した血漿を本剤の製造に使用している。万一、原料血漿に血液媒介ウイルスが混入したとしても、各種モデルウイルスを用いたウイルスクリアランス試験成績から、本剤の製造工程において不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。	

JBPO 2013-003

Guidance for Industry

Implementation of an Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Source Plasma

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2013

Contains Nonbinding Recommendations

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Guidance for Industry

Implementation of an Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Source Plasma

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance recognizes the standardized full-length and abbreviated donor history questionnaires and accompanying materials, version 1.2 dated September 2012, prepared by the Plasma Protein Therapeutics Association (PPTA) as an acceptable mechanism that is consistent with the Food and Drug Administration's (FDA's) requirements and recommendations for collecting Source Plasma donor history information. In the future, we, FDA, may recognize other Source Plasma donor history questionnaires and accompanying materials as acceptable. We intend to make the current recognized versions of the Source Plasma donor history questionnaires and accompanying materials (referred to as "SPDHQ documents") available on the FDA website.

The SPDHQ documents will provide blood establishments that collect Source Plasma (referred to as "manufacturers" or "you"), with a specific process for administering questions to Source Plasma donors (referred to as "donors") to determine their eligibility to donate. We are using the term "eligibility" in this guidance to refer to the donor suitability requirements described in Title 21 Code of Federal Regulations 640.63 (21 CFR 640.63). Acceptable SPDHQ documents are those documents that FDA has determined will provide Source Plasma manufacturers with one means of obtaining donor history information from a Source Plasma donor to determine if the donor is eligible consistent with the requirements in 21 CFR 640.63.

This guidance also advises Source Plasma manufacturers who choose to implement the acceptable SPDHQ documents on how to report the manufacturing change consisting of the implementation of the SPDHQ under 21 CFR 601.12 (§ 601.12).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, these guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements

are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 640.63(a) requires the eligibility of Source Plasma donors to be determined on the day of collection. (We interpret "day of collection" to permit clarifying a donor's response to the donor history questionnaire or obtaining omitted responses to questions within 24 hours of the time of collection.[1]) Such determination is intended to ensure a donor's overall good health and prevent transmission of diseases transmissible by blood and blood components (21 CFR 640.63(a-d)). A donor's eligibility to donate blood and blood components is determined in part by a physical assessment and the donor's answers to questions concerning medical history and risk factors for diseases transmissible by blood and blood components. The donor screening interview is especially important in identifying risks for diseases and conditions for which there are no adequate laboratory tests or for which tests are unable to identify early stage or window period infection.

The first formal uniform questionnaire developed for the purpose of blood donor screening was implemented nearly sixty years ago (Ref. 1). Though the donor interview process is helpful in excluding ineligible donors, errors in this process do occur because some information may not be understood or captured during the screening process (Ref. 2). As noted during workshops sponsored by FDA to discuss this issue, the blood donor screening process should consider such factors as question complexity, donor recall ability, donor health and safety, donor satisfaction and willingness to return, any further processing which a product may undergo prior to use, and risk to the end user/recipient of blood and blood components (Refs. 3 and 4). Strategies such as using self-administered computer-assisted and abbreviated questionnaires have been suggested as approaches to improve donor understanding and satisfaction over what some view as a lengthy and time-consuming process, particularly for frequent donors (Refs. 3 through 5). FDA has previously issued a guidance documented entitled "Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires," dated July 2003 (Streamlining Donor Interview guidance) explaining how blood and plasma establishments may simplify the donor screening process by allowing certain donors to use self-administered donor questionnaires (Ref. 6).

The full-length and abbreviated questionnaires are designed to be implemented together. For example, if you choose to implement the Abbreviated PPTA Donor History Questionnaire, you should also implement the Full-Length PPTA Donor History Questionnaire as described in the

[1] See FDA guidance documented entitled "Guidance for Industry: Recommendations for Blood Establishments: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application," dated November 2010 for additional information on donor suitability procedures, available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm235785.htm.

Directions for Use. Both the full-length and abbreviated questionnaires are designed to be administered either by Source Plasma establishment personnel or self-administered with follow-up by establishment personnel.

The SPDHQ documents include the following materials and are intended to be used in their entirety, with the exceptions noted in Section IV.A.2.:

- Full-Length Donor History Questionnaires
  - Questionnaire I – to be used by Source Plasma establishments that use an approved test to detect HIV-1 Group O variant.
  - Questionnaire II – to be used by Source Plasma establishments that do not use an approved test to detect HIV-1 Group O variant.
- Full-Length PPTA Donor History Questionnaire Directions for Use – includes glossary, flow charts and references; describes how questions can be administered; and contains follow-up questions to further evaluate a potential donor's response to "capture questions."[2]
- Abbreviated Donor History Questionnaire – to be used by frequent Source Plasma donors.
- Abbreviated PPTA Donor History Questionnaire Directions for Use – includes glossary, flow charts and references, describes which donors may complete the questionnaire and how the questions can be administered, and contains follow-up questions to further evaluate a potential donor's response to capture questions.
- Medication List – contains a list of medications that may serve as a basis for donor deferral.
- Risk Posters – educate the donor about risks and conditions that are a basis for donor deferral.
  - Poster I – to be used by Source Plasma establishments that use an approved test to detect HIV-1 Group O variant.
  - Poster II – to be used by Source Plasma establishments that do not use an approved test to detect HIV-1 Group O variant.
- Travel Posters – identify countries endemic for diseases that can be transmitted by blood and blood components.
  - Travel Poster I – to be used by Source Plasma establishments that use an approved test to detect HIV-1 Group O variant.
  - Travel Poster II – to be used by Source Plasma establishments that do not use an approved test to detect HIV-1 Group O variant.

III. RECOGNITION OF PPTA SPDHQ DOCUMENTS

We find the SPDHQ documents (version 1.2) to be acceptable for use in screening Source Plasma donors. These documents are consistent with FDA requirements and recommendations

[2] Capture questions ask general questions about a potential donor's history and are followed up by more specific questions if needed.

related to donor eligibility interviews, subject to the following exception. The SPDHQ documents contain questions related to the following donor medical history issues for which we currently do not have requirements or recommendations: cancer; organ, tissue, or bone marrow transplant; bone or skin graft; and pregnancy. By recognizing the acceptable SPDHQ documents as one way to satisfy FDA's regulatory requirements, we are not requiring or recommending that donors be screened or deferred for these issues. If you choose to implement the acceptable SPDHQ documents and omit these questions, you would still be in compliance with FDA requirements.

While we recognize that the acceptable SPDHQ documents provide an effective tool for screening donors, we do not require that you implement the acceptable SPDHQ documents. You may continue to use the full-length and abbreviated donor history questionnaires and accompanying materials developed by your establishment and previously approved by FDA. These materials may include procedures and wording that are different from those in the SPDHQ documents. In the future, you may implement, consistent with § 601.12, new procedures and materials that differ from those in SPDHQ documents (Ref. 7).

IV. REPORTING TO FDA THE IMPLEMENTATION OF ACCEPTABLE DONOR HISTORY QUESTIONNAIRES AND ACCOMPANYING MATERIALS

As indicated above, we recommend that the full-length and abbreviated questionnaires be used together. For example, if you choose to implement the Abbreviated PPTA Donor History Questionnaire, we recommend that you also implement the Full-Length PPTA Donor History Questionnaire.

A. Implementation of the Acceptable SPDHQ Documents

You must report the implementation of the acceptable SPDHQ documents to FDA under § 601.12 as follows:

1. If the acceptable SPDHQ documents are implemented without modifications and in their entirety as a complete process for administering questions to Source Plasma donors, the change is considered to be minor, with a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. You must report such changes to FDA in your annual report under § 601.12(d), noting the date the process was implemented. If donors will be allowed to self-administer the acceptable SPDHQ documents, see section IV.B.

2. If the acceptable SPDHQ documents are implemented in their entirety, but modified (a) by adding additional, more restrictive selection criteria that are specific to your establishment; or (b) by omitting questions related to cancer; organ, tissue, or bone marrow transplant; bone or skin graft; and pregnancy, which FDA has not required or recommended for determining donor eligibility, the changes are considered to be minor. Report such changes to FDA in your annual report under § 601.12(d), noting

the date the process was implemented and describing the additional criteria or the questions that were omitted from your questionnaire.

3. If you make changes to the format or wording in the SPDHQ flow charts but the content remains consistent with FDA required/recommended donor deferral criteria or if you adopt stricter donor deferral criteria, the changes are considered to be minor. You must report such changes to FDA in your annual report under § 601.12(d), noting the date the process was implemented and describing how you modified the acceptable SPDHQ documents.

4. If the acceptable SPDHQ documents are implemented in their entirety, but modified by reformatting any of the acceptable SPDHQ documents (other than the flow charts) to be consistent with your current process, the changes are considered minor, provided you do not change the wording and the order of content in the acceptable SPDHQ documents. Report such changes to FDA in your annual report under § 601.12(d), noting the date the process was implemented and describing how you modified the acceptable SPDHQ documents.

5. Donor screening is important to the safety of blood components and screening procedures have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of blood and blood components as they may relate to the safety or effectiveness of the product. Therefore, the implementation of the acceptable SPDHQ documents that have been modified other than as specifically described in sections IV.A.2-4, will be a major change. If you wish to implement the acceptable SPDHQ documents modified in a manner other than as described in sections IV.A.2-4, you must report such changes as a Prior Approval Supplement (PAS) under § 601.12(b). We recommend that you include the following in the submission:

    a. FDA Form 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" which may be obtained at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm;
    b. A cover letter describing the request and the contents of the submission;
    c. A written SOP describing the donor questions and questionnaire process; and
    d. The donor history questionnaires and accompanying document(s). Please highlight the modifications.

For assistance in preparing the supplement, please refer to FDA's guidance entitled "Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the Form FDA 356h 'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use,'" dated May 1999 (Ref. 8).

B. Implementation of Self-Administered Acceptable SPDHQ Documents

In July 2003, we issued the Streamlining Donor Interview guidance (Ref. 6), advising licensed blood establishments to submit procedures for self-administering the donor history questionnaire to FDA as a Changes Being Effected in 30 days supplement (CBE30) under § 601.12(c). We determined in the Streamlining Donor Interview guidance that a CBE30 was an appropriate supplement to ensure that controls were in place to manage this process. However, we have since determined that when acceptable DHQ documents include instructions for controlling the self-administration process, such as in the SPDHQ Directions for Use, this change may be reported in an annual report or, in some situations, as a CBE30, as described in IV.B.1 and IV.B.2 below. These recommendations modify those stated in the Streamlining Donor Interview guidance. Licensed manufacturers planning to implement self-administration of a questionnaire other than the acceptable SPDHQ documents should continue to consult the Streamlining Donor Interview guidance (Ref. 6).

Licensed manufacturers must report implementation of self-administered acceptable SPDHQ documents under § 601.12 as follows:

1. If you choose to implement self-administration of the acceptable SPDHQ documents using the written form or audio/visual presentation methods described in the acceptable SPDHQ documents, this is considered a minor change. Report such a change to FDA in your annual report under § 601.12(d), noting the date the process was implemented.

2. If you choose to implement the acceptable SPDHQ documents using a computer-assisted interactive interview procedure, report this change to FDA as a Supplement – Changes Being Effected in 30 Days (CBE30) under § 601.12(c). This change presents a moderate potential to adversely affect the identity, strength, quality, purity, or potency of blood and blood components, as they may relate to the safety or effectiveness of the product, because of concerns that the presentation of the questions and information may not be easily readable in all conditions and by all potential users. Additionally, implementation for the first time of a computer-assisted interactive interview procedure may raise new issues that should be evaluated, such as the management of electronic records. Therefore, we cannot conclude at this time that the implementation of a computer-assisted interactive interview procedure will be a minor change.

For assistance in implementing and reporting the use of self-administered questionnaires other than as described above, and for preparing the supplement for the computer-assisted interactive interview procedure, see the Streamlining Donor Interview guidance (Ref. 6).

V. RECOGNITION AND IMPLEMENTATION OF FUTURE ACCEPTABLE SPDHQ DOCUMENTS

In the future, we may issue regulations or guidance documents concerning donor deferrals when we identify new infectious diseases, medical conditions, behaviors, geographic exposures or medications that have the potential to affect the donor's safety or the safety, purity, and potency of Source Plasma. Implementation of new safeguards would change your donor interview SOPs,

and involve amending accepted SPDHQ documents (typically by adding a question at the end of the questionnaire in the area designated for additional questions or by implementing new or revised SPDHQ documents). If you do not use the acceptable SPDHQ documents, this would involve amending your own questionnaire. We anticipate that in the event we recommend a new donor deferral criterion, we will, in the same guidance, provide recommendations concerning implementing and reporting to FDA the manufacturing changes associated with this change in procedure. If revised SPDHQ documents are available and found acceptable, we also intend to recognize those SPDHQ documents as acceptable in the guidance document addressing the donor deferrals. We intend to make all acceptable SPDHQ documents available on the FDA website.

We recommend that you have a procedure in place for implementing updated donor questionnaire documents in all your facilities.

VI. FOR MORE INFORMATION

If you have questions regarding this guidance and FDA policies for implementing the acceptable SPDHQ documents, call OCOD at the numbers provided above.

If you have questions regarding the SPDHQ documents, contact PPTA by phone at 202-789-3100, fax at (410) 263-2298 or online at http://www.pptaglobal.org/contact/default.aspx.

You may view the SPDHQ documents that FDA has recognized as acceptable on the FDA website at http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/ucm255235.htm.

VII. REFERENCES

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5. Strategies for Increasing the U.S. Blood Supply. HHS, PHS Working Group. Available athttp://www.fda.gov/ohrms/dockets/ac/99/backgrd/3548b1i.pdf.
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7. FDA Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, July 2001. Available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076729.htm.
8. FDA Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use," May 1999. Available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077087.htm.

Full-length Donor History Questionnaire I – Source Plasma Industry

This document is one component of the full-length PPTA donor history questionnaire documents to be used by source plasma organizations that use an approved test for antibodies to HIV that detect HIV-1 Group O. The full-length PPTA donor history questionnaire documents must be used collectively.

Full-length Donor History Questionnaire I – Source Plasma Industry

	Yes	No	
Are you			
1. Feeling healthy and well today?	❑	❑	
2. Currently taking an antibiotic or other medication for infection?	❑	❑	
3. Currently taking any other medications?	❑	❑	
Please read the medication list.			
4. Are you now taking or have you ever taken any medications on the medication list?	❑	❑	
Please review the Risk Poster			
5. Did you review the Risk Poster?	❑	❑	
6. Do you have any questions about anything mentioned on the Risk Poster?	❑	❑	
In the past **six weeks**			
7. Female donors: Have you been pregnant or are you pregnant now? (Males: check "I am male.")	❑	❑	❑ I am male
In the past **two months**			
8. Have you had any vaccinations or other shots?	❑	❑	
9. Have you had contact with someone who had a smallpox vaccination?	❑	❑	
10. Have you donated whole blood, platelets or plasma at another center?	❑	❑	
In the past **four months**			
11. Have you donated a double unit of red cells using an apheresis machine?	❑	❑	
In the past **12 months,** have you			
12. Had a blood transfusion?	❑	❑	
13. Received during surgery bone, tissue or skin?	❑	❑	
14. Come into contact with someone else's blood?	❑	❑	
15. Had an accidental needle-stick?	❑	❑	
16. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?	❑	❑	
17. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?	❑	❑	
18. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything <u>not</u> prescribed by their doctor?	❑	❑	
19. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates?	❑	❑	
20. Female donors: had sexual contact with a male who has ever	❑	❑	❑ I am

had sexual contact with another male? (Males: check "I am male.")			male
21. Had sexual contact with a person who has hepatitis?	❑	❑	
22. Lived with a person who has hepatitis?	❑	❑	
23. Gotten a tattoo or had one touched-up?	❑	❑	
24. Had an ear or body piercing?	❑	❑	
25. Had or been treated for syphilis or gonorrhea?	❑	❑	
26. Been in juvenile detention, lockup, jail, or prison for more than 72 hours?	❑	❑	
From 1980 through 1996			
27. Did you spend time that adds up to three months or more in the United Kingdom? (Review map of UK Countries on the travel poster)	❑	❑	
28. Were you a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military?	❑	❑	
From 1980 to the present, did you			
29. Spend time that adds up to four years or more in France?	❑	❑	
30. Receive a blood transfusion in the United Kingdom or France? (Review map of UK Countries on the travel poster)	❑	❑	
From 1977 to the present, have you			
31. Received money, drugs, or other payment for sex?	❑	❑	
32. Male donors: had sexual contact with another male, even once? (Females: check "I am female.")	❑	❑	❑ I am female
Have you **EVER**			
33. Had a positive test for the HIV/AIDS virus?	❑	❑	
34. Used needles to take drugs, steroids, or anything not prescribed by your doctor?	❑	❑	
35. Used clotting factor concentrates?	❑	❑	
36. Had hepatitis?	❑	❑	
37. Had a transplant such as organ or bone marrow?	❑	❑	
38. Received a dura mater (or brain covering) graft?	❑	❑	
39. Had any type of cancer, including leukemia?	❑	❑	
40. Had any problem with your heart or lungs?	❑	❑	
41. Had any problem with your liver or kidneys?	❑	❑	
42. Had a bleeding condition or a blood disease?	❑	❑	
43. Have any of your relatives had Creutzfeldt-Jakob disease?	❑	❑	

Additional Questions:

Full-length Donor History Questionnaire II – Source Plasma Industry

This document is one component of the full-length PPTA donor history questionnaire documents to be used by source plasma organizations that do not use an approved test for antibodies to HIV that detects HIV-1 group O. The full-length PPTA donor history questionnaire documents must be used collectively.

Full-length Donor History Questionnaire II – Source Plasma Industry

	Yes	No	
Are you			
1. Feeling healthy and well today?	❑	❑	
2. Currently taking an antibiotic or other medication for infection?	❑	❑	
3. Currently taking any other medications?	❑	❑	
Please read the medication list.			
4. Are you now taking or have you ever taken any medications on the medication list?	❑	❑	
Please review the Risk Poster			
5. Did you review the Risk Poster?	❑	❑	
6. Do you have any questions about anything mentioned on the Risk Poster?	❑	❑	
In the past **six weeks**			
7. Female donors: Have you been pregnant or are you pregnant now? (Males: check "I am male.")	❑	❑	❑ I am male
In the past **two months**			
8. Have you had any vaccinations or other shots?	❑	❑	
9. Have you had contact with someone who had a smallpox vaccination?	❑	❑	
10. Have you donated whole blood, platelets or plasma at another center?	❑	❑	
In the past **four months**			
11. Have you donated a double unit of red cells using an apheresis machine?	❑	❑	
In the past **12 months,** have you			
12. Had a blood transfusion?	❑	❑	
13. Received during surgery bone, tissue or skin?	❑	❑	
14. Come into contact with someone else's blood?	❑	❑	
15. Had an accidental needle-stick?	❑	❑	
16. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?	❑	❑	
17. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?	❑	❑	
18. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?	❑	❑	
19. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates?	❑	❑	
20. Female donors: had sexual contact with a male who has ever	❑	❑	❑ I am male

had sexual contact with another male? (Males: check "I am male.")			
21. Had sexual contact with a person who has hepatitis?	❑	❑	
22. Lived with a person who has hepatitis?	❑	❑	
23. Gotten a tattoo or had one touched-up?	❑	❑	
24. Had an ear or body piercing?	❑	❑	
25. Had or been treated for syphilis or gonorrhea?	❑	❑	
26. Been in juvenile detention, lockup, jail, or prison for more than 72 hours?	❑	❑	
From 1980 through 1996			
27. Did you spend time that adds up to three months or more in the United Kingdom? (Review map of UK Countries on the travel poster)	❑	❑	
28. Were you a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military?	❑	❑	
From 1980 to the present, did you			
29. Spend time that adds up to four years or more in France?	❑	❑	
30. Receive a blood transfusion in the United Kingdom or France? (Review map of UK Countries on the travel poster)	❑	❑	
From 1977 to the present, have you			
31. Received money, drugs, or other payment for sex?	❑	❑	
32. Male donors: had sexual contact with another male, even once? (Females: check "I am female.")	❑	❑	❑ I am female
Have you **EVER**			
33. Had a positive test for the HIV/AIDS virus?	❑	❑	
34. Used needles to take drugs, steroids, or anything <u>not</u> prescribed by your doctor?	❑	❑	
35. Used clotting factor concentrates?	❑	❑	
36. Had hepatitis?	❑	❑	
37. Had a transplant such as organ or bone marrow?	❑	❑	
38. Received a dura mater (or brain covering) graft?	❑	❑	
39. Had sexual contact with anyone who was born in or lived in Africa? (review map of Africa on the travel poster)	❑	❑	
40. Been in Africa? (review map of Africa on the travel poster)	❑	❑	
41. Had any type of cancer, including leukemia?	❑	❑	
42. Had any problem with your heart or lungs?	❑	❑	
43. Had any problem with your liver or kidneys?	❑	❑	
44. Had a bleeding condition or a blood disease?	❑	❑	
45. Have any of your relatives had Creutzfeldt-Jakob disease?	❑	❑	

Additional Questions:

This document is one component of the full-length PPTA donor history questionnaire documents. This full length directions for use contains information for all source plasma organization regardless of HIV-1 Group O testing capabilities. The full length PPTA Donor History Questionnaire Documents must be used collectively.

Source Plasma Full-Length PPTA Donor History Questionnaire Directions for Use

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Source Plasma Full-Length PPTA Donor History Questionnaire
Directions for Use

Purpose: The PPTA Donor History Questionnaire (PPTA DHQ) Directions for Use is a guideline designed as an aid for the plasma sourcing organizations to use in the development of specific company policies and training materials related to donor eligibility. The PPTA DHQ Directions for Use does not replace the company policy for determining donor suitability. Each source plasma collection organization must have a standard operating procedure (SOP) related to donor suitability to be used in conjunction with the Directions for Use. The Directions for Use does not replace an SOP for determining donor suitability. Both the Directions for Use and the SOP must be available to staff performing health histories. Alternately, the Directions for Use contents may be transcribed into the SOP.

Introduction: The following documents are included in this package: Two Full-Length PPTA Donor History Questionnaires (PPTA DHQ[1]), two Risk Posters, two Travel Posters[1], and a Medication List. The PPTA DHQ must be administered on the date of donation as per Title 21, Code of Federal Regulations, Part 640.63(b). The plasmapheresis center staff must provide to the prospective donor the Risk Poster, the Travel Poster, and the Medication List, and any other material that the plasmapheresis center's company policy requires to be used with the PPTA DHQ. These documents should be incorporated into the company's donor eligibility process, which includes the physical examination and informed consent (each having its own educational information), in a manner that conveys the importance of the donor history questions in protecting the donor's health and the safety of the plasma supply and the responsibility of the donor to provide accurate information. The Risk Poster was designed to replace the "AIDS Bulletin" which is currently used by plasmapheresis centers to educate donors about HIV infection and AIDS. Also, for additional donor education, the Risk Poster, the Travel Poster, and the Medication List may be prominently displayed in designated areas.

Methods of Administration: The method of administration of the PPTA DHQ should be in accordance with the plasmapheresis center's company policy.

The questionnaires were designed to be used by a health historian in direct donor questioning or by self-administration, with follow-up review (if necessary) by a trained donor historian. A trained historian should be available to the prospective donor to answer any questions concerning eligibility or the donation process. Donor screening is an active process involving open communication between donors and trained donor historians. Donors should be encouraged to voice questions and concerns at any time during the screening and donation process. Company policies should require that donors be asked if they have questions and if they have had their questions answered. This does not need to be a specific question on the questionnaire, but may be

[1] The questionnaire, risk poster or travel poster used is dependent on whether the plasma sourcing organization uses a test to detect HIV-1 Group O.

incorporated into the donor eligibility process, including the physical examination, and/or put into the informed consent.

Self-administration may occur in a computer-assisted self interview (CASI) process. With CASI administration, the Risk Poster, Travel Poster and Medication List can be provided in hard-copy form or in an electronic format. Formatting can be adjusted as long as the order, content and wording are unchanged. Questions directed at one sex can be omitted from sex-specific questionnaires. As stated above, a trained historian should be available to a prospective donor to answer any questions concerning eligibility or the donation process. For further instructions, refer to the CASI manufacturer's instructions and operator's manual.

If questionnaire is administered by a health historian in direct donor questioning, the heading before each section should be stated along with the question to ensure the specific timeframe or instruction is clear.

Deferral decisions can be made any time during the administration of the questionnaire. Individual company policies will dictate whether an eligibility decision can be made prior to completing the entire questionnaire. However, it is recommended that the questionnaire be completed before making a determination of eligibility since some deferrals are temporary, but others are indefinite/permanent. Depending on the sequence of questions, a donor could be deferred temporarily, only to return at a later date and discover that he/she is permanently deferred due to the answer to another question that was not answered on the previous visit.

Full-Length PPTA DHQ Format: The Full-Length PPTA DHQ questions were composed for ease of understanding by the prospective plasma donor. The PPTA DHQ questions are grouped by time period beginning with a question about "today" and ending with questions relating to "have you ever". The questions are therefore grouped under headings. Depending on the method of administration, e.g., oral administration by a health historian, the heading may need to be repeated with each question. The PPTA DHQ questions and format were evaluated for comprehension; therefore, the wording and the order of the questions should not be changed.

Additional Questions: Plasma sourcing organizations may choose to add "local" additional questions to the end of the PPTA DHQ. If a collection facility chooses to add "local" questions they should be grouped at the end of the DHQ in the area designated for additional questions. Facilities should also use this area to incorporate new questions that are necessary due to new policies recommended by FDA and/or PPTA. This area should be used until such questions can be formally incorporated into the DHQ materials by PPTA. The questions will remain in the additional questions section until a revised strategy for incorporation is found acceptable by FDA. If the new question(s) result from FDA guidance, incorporation and implementation of the new question(s) should be consistent with the current thinking in the FDA guidance document that discussed the new question(s) or deferral. In order to delineate the proper order of the questions PPTA will renumber the questions as needed when questions are added or deleted. Plasma sourcing organizations may choose to use a different numbering system, but the order of the questions should not be changed.

Plasma sourcing organizations should use the Medication List, as is, to elicit whether a donor is currently taking or has taken the medications on the list. Information on other medications may be provided as an appendage or separate document, as appropriate.

Questions to detect donors at risk for HIV Group O: The questions related to Africa are recommended by FDA to identify donors who may be at risk for HIV Group O infections. Plasma sourcing organizations utilizing an HIV test that has been approved by FDA for donor screening to include a claim for detection of group O viruses may delete these questions from their screening questionnaire and may renumber the remainder of the questions (and related documents such as flow charts). All other plasma collection centers must continue to use these questions as formatted. To assist in the ease of administration of the questions related to Africa, PPTA created two sets of documents: (I) to be used by those who use a test approved to detect HIV-1 Group O and (II) those that do not. Therefore, there are two Risk Posters available and two Travel Posters available. The posters that may be used are dependent on whether the source plasma organization uses an approved test for detection of HIV-1 Group O. The appropriate version of the risk and travel poster that is chosen should be used in its entirety.

Capture Questions: The PPTA DHQ uses “capture questions” that may require donor historian intervention or follow up. Capture questions are general questions that when answered “yes” require additional questions or information to determine donor suitability. Some follow-up questions are included in the PPTA DHQ Directions for Use but since specific donor eligibility criteria may vary from one plasma sourcing organization to another, an affirmative response to some questions may require consultation with the plasmapheresis center’s company policy.

Attention Questions: In order to assure that donors who self-administer a paper PPTA DHQ maintain focus, several “attention” questions are included. An example of an attention question is: “In the past 6 weeks, have you been pregnant or are you pregnant now?” (Males check “I am male”) An inappropriate answer to the question would be a male answering “yes” or “no.” Each plasma sourcing organization must define the action of the donor historian when a donor inappropriately answers the attention questions. Attention questions may not be necessary when using other techniques to assure donor focus, such as CASI or oral screening by a donor historian.

Full-Length PPTA DHQ Administration Frequency: The Full-Length PPTA DHQ was designed as a stand alone questionnaire that may be used at each donation. It may also be used in conjunction with an abbreviated form for frequent donors. Use of the full-length questionnaire in conjunction with the abbreviated questionnaire is discussed in the PPTA Abbreviated Donor History Questionnaire Directions for Use.

PPTA DHQ Directions for Use Flow Chart Format: The PPTA DHQ Directions for Use is modular and uses flow-charting to guide organizations through the donor questionnaire process. Each question is a complete section that begins on a new page so that changes to the PPTA DHQ and the Abbreviated PPTA DHQ can be easily

modified in the PPTA DHQ Directions for Use. Each section contains the following information:

Question: Question number and the question

Donor Eligibility: This section provides additional information to the donor historian on donor eligibility with respect to each question.

Note: Optional field that provides additional relevant information relating to the donor question.

Flow Chart: Each question is flow-charted using standard flow-charting symbols.

Square: Statement

Diamond: Question/decision point

Oval: Action

Arrow: Move to the next question.

Each question ends with an arrow that indicates to "move to the next question"; however, plasmapheresis centers must follow their established policies to determine if the donor suitability process is completed when it is known that the donor will be deferred.

Donor Deferrals: For some questions, a "yes" answer calls for a required donor deferral either indefinitely or for a specified period of time. A required deferral is designated in the flow chart by the Action "Defer donor" followed by "indefinitely" or with the time period established by FDA regulations/recommendations or "per company policy". For the latter, the organizations will use their established policies and procedures to determine if and when the donor may be eligible to return. In some cases, such as a donor providing a history of having had cancer, company policy will dictate the follow-up questions that are required to determine donor eligibility. Evaluation "per company policy" may deem the donor eligible to donate without a period of deferral. Additionally, when a question provides information to support deferral of the donor "per company policy", "per company policy" cannot be less restrictive than what is clearly delineated in FDA policy.

Documentation: Answers to the questions that are cause for donor deferral must be documented according to the plasmapheresis center's company policy. Each plasmapheresis center's company policy must define how the donor responses to the follow up questions will be documented.

Maintenance/Change Control: The Plasma Protein Therapeutics Association (PPTA) is responsible for the maintenance of the PPTA Donor History Questionnaire project documents. Documents are posted on the PPTA website. Periodically the PPTA Donor

History Questionnaire, the accompanying documents or the directions for use will be updated or revised by the PPTA DHQ task force as required for compliance with regulatory and accrediting agencies. PPTA member companies will be notified of the changes and timeline for implementation in existing publications and on the PPTA website, and all updated documents will be made available on the website. It is the responsibility of plasmapheresis centers to make changes in their forms, procedures and processes to incorporate these revisions within the specified time.

GLOSSARY

The following terms are defined in the context of their use in the PPTA Donor History Questionnaire.

DONOR CLASSIFICATION

Applicant Donor – All individuals presenting themselves who have not been previously qualified as a donor within the past six (6) months.

Qualified Donor – All individuals who have been qualified for continued donations by successfully passing two donor medical history screenings and required viral testing.

QUESTIONNAIRE TERMS

Attention Question – Questions in the Donor History Questionnaire that are designed to test if the donor is paying attention. EXAMPLE: In the past six weeks, have you been pregnant or are you pregnant now? (Males check: "I am Male")

Capture Question – A question that covers a broad topic. When an affirmative answer is given, additional follow-up questions to elicit additional information are asked by the donor historian. EXAMPLE: Have you ever been to Africa? If the donor answers yes, additional questions must be asked.

Self-administered Questionnaire – A questionnaire that the donor completes on his/her own, followed by donor health historian review.

CASI – Computer-assisted Self-interviewing system. Most often the system consists of an interactive computer screen. Questions are asked in written format, with or without graphics and audio.

TYPES OF CONTACT

Contact with Blood – (1) a needlestick or other sharps injury from an instrument that has been used on any individual or patient; (2) exposure to non-intact skin (e.g., skin that is chapped, abraded, or afflicted with dermatitis); (3) a human bite that breaks the skin; (4) exposure to eye, nose, or mouth i.e., the mucous membranes.

Sexual Contact – The meaning of the words "sexual contact with" and "sex" are identical, and apply to any of the following activities, whether or not a condom or other protection was used: (1) Vaginal sex (contact between penis and vagina); (2) Oral sex (mouth or tongue on someone's vagina, penis, or anus); (3) Anal sex (contact between penis and anus).

Close Contact with Smallpox Vaccination Site – Touching the vaccination site, including the bandages covering the vaccination site; touching/handling materials that might have come into contact with an unbandaged vaccination site including clothing, towels, and bedding.

Lived With – Residing in the same dwelling in which kitchen and bathroom facilities are shared. Donors that have the same address would not be considered under the term "lived with" unless kitchen and bathroom facilities are shared.

TYPES OF DEFERRAL

Indefinite Deferral – Prospective donor is unable to donate blood for someone else for an unspecified period of time due to current regulatory requirements. EXAMPLE: A prospective donor who states that they lived in England for 1 year in 1989 would be deferred indefinitely. This donor would not be able to donate blood until the current requirement changes.

Permanent Deferral – Prospective donor will never be eligible to donate blood for someone else. EXAMPLE: A prospective donor states that he/she has Hepatitis C. Additionally, some permanent deferrals may result from the testing performed on a previous donation.

Temporary Deferral – Prospective donor is unable to donate blood for a limited period of time. EXAMPLE: A prospective donor who has received a transfusion within the last 12 months would be deferred for 12 months from the date of the transfusion.

References

Donor qualification requirements are located in Title 21, Code of Federal Regulations, Subpart G—Source Plasma, and in PPTA voluntary standards in its International Quality Plasma Program (IQPP).

Additional donor qualification requirements may be found in FDA memoranda and guidance:

FDA Memorandum, December 12, 1991: Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing.

FDA Memorandum, April 23, 1992: Revised Recommendations for the Prevention of HIV Transmission by Blood and Blood Products.

FDA Memorandum, April 23, 1992: Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma, and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti HCV) in Blood Establishments.

FDA Memorandum, July 28, 1993: Deferral of Blood and Plasma Donors Based on Medications.

FDA Memorandum December 22, 1993: Donor Suitability Related to Laboratory Testing For Viral Hepatitis and a History of Viral Hepatitis.

FDA Memorandum, June 8, 1995: Recommendations for the Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma.

FDA Memorandum, December 14, 1995: Donor Deferral Due to Red Blood Cell Loss During Collection of Source Plasma.

FDA Guidance, August 2009: Recommendations for Management of Donors at Increased Risk for Human Immunodeficiency Virus Type 1 (HIV-1) Group O Infection

Blood Products Advisory Committee Meeting June 16, 2000: Update on Sexual Transmission of HCV.

FDA Guidance, February 2001: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods.

FDA Guidance, May 2010: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products.

Avodart Consumer Information, January 14, 2003:
www.fda.gov/cder/consumerinfo/druginfo/avodart.htm.

AABB Pulse Points No. 555, January 14, 2003: Association Bulletin #30-02: Donor Deferral Related to Use of AVODART™ (dutasteride).

FDA Guidance, December 2002: Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients.

FDA Guidance, February 4, 2003 (corrected): Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients.

FDA Guidance, July 3, 2003: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires.

FDA Guidance, September 16, 2003: Revised Recommendations for the Assessment of Donor Suitability and Blood Product Safety in Cases of Suspected Severe Acute Respiratory Syndrome (SARS) or Exposure to SARS.

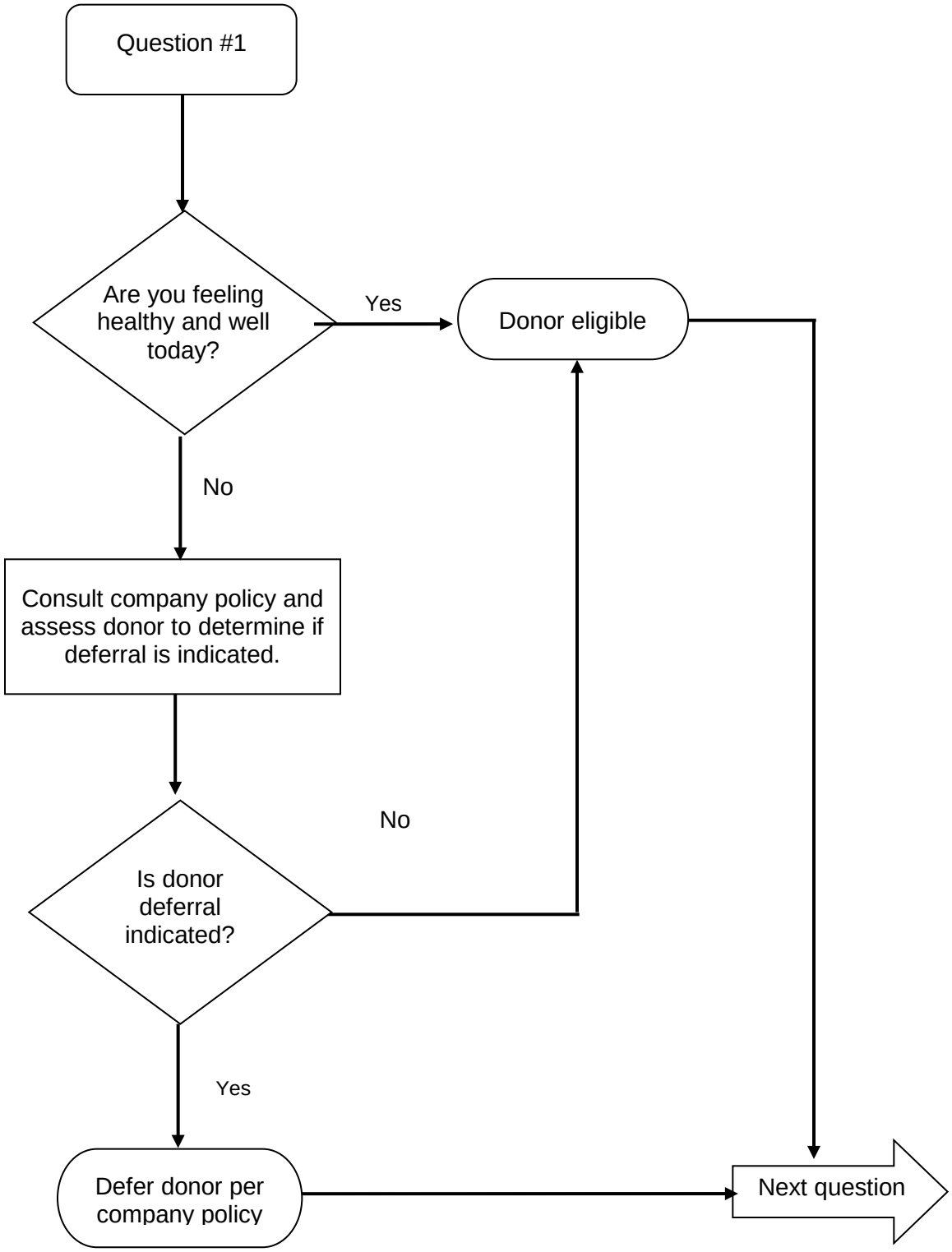
FDA Guidance, October 27, 2006: Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components.

FDA Guidance, June 20, 2007: Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs.

FDA Guidance, May 2010: Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry.

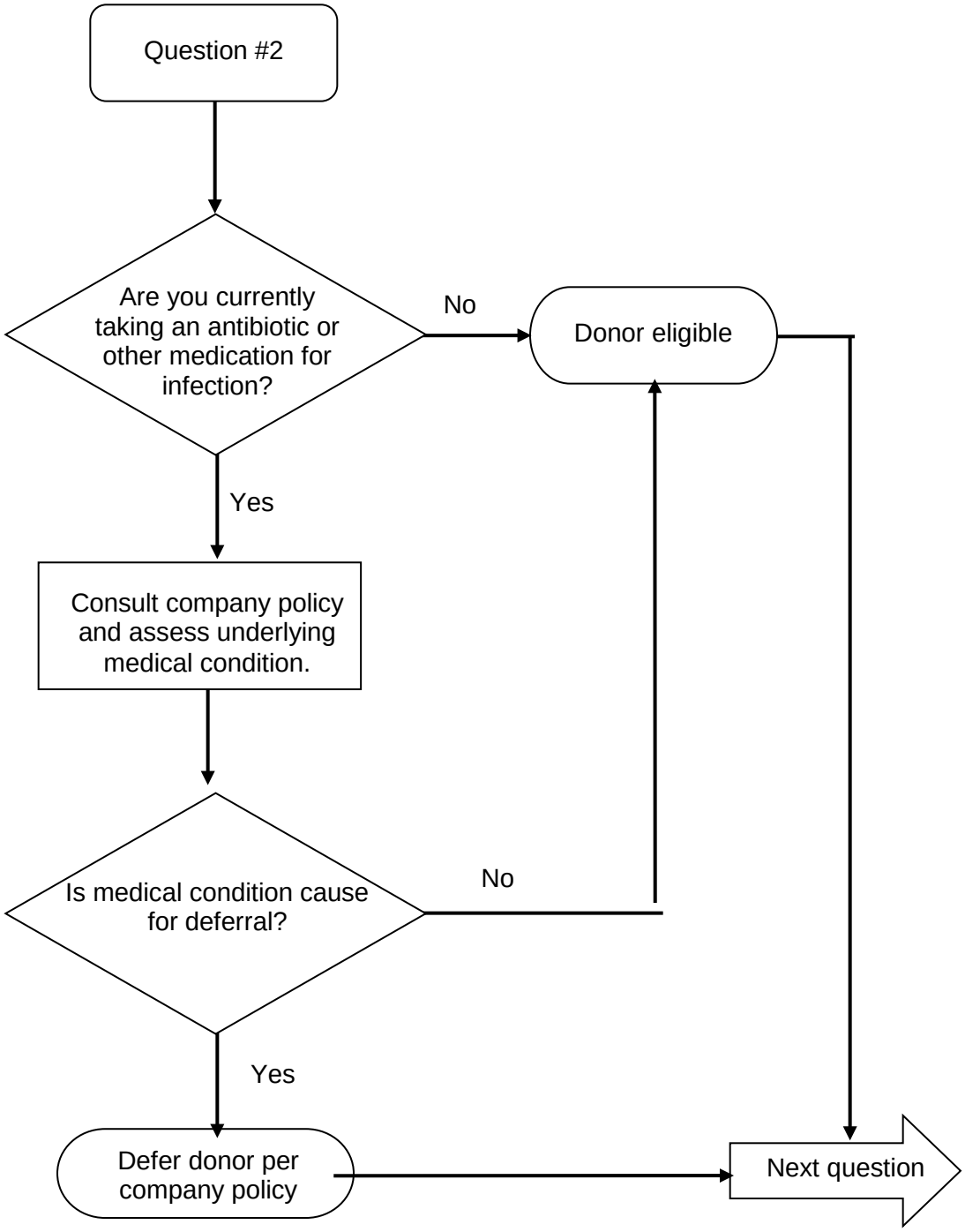
Question #1: Are you feeling healthy and well today?

Donor Eligibility: A donor should be free of infectious diseases on the day of donation. Donors who are not in good health should not donate until it is determined that the underlying condition is not cause for deferral.



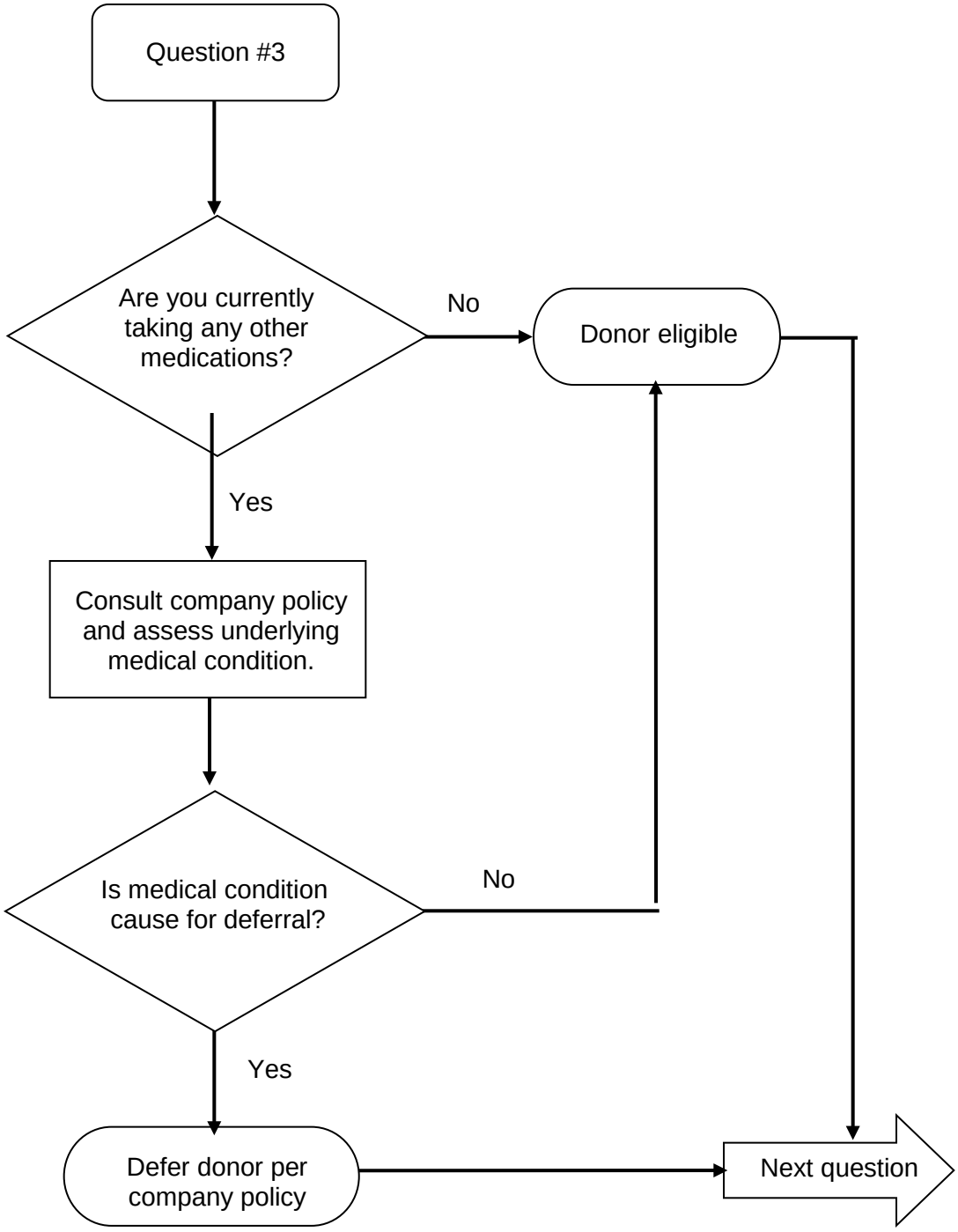
Question #2: Are you currently taking an antibiotic or other medication for infection?

Donor Eligibility: A donor with an infection should not donate. The reason for antibiotic use must be evaluated to determine if the donor has a bacterial infection that could be transmissible by blood.



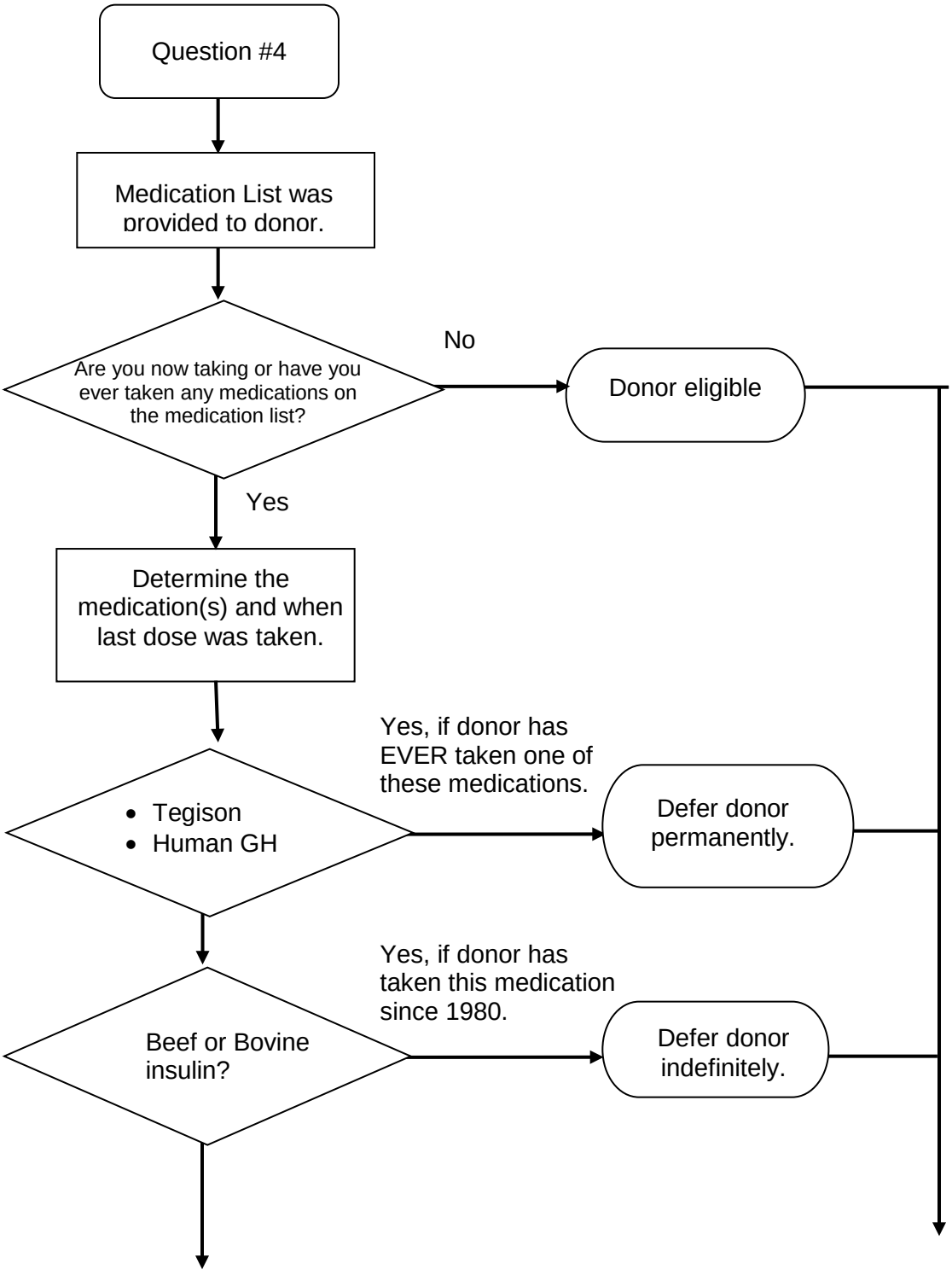
Question #3: Are you currently taking any other medications?

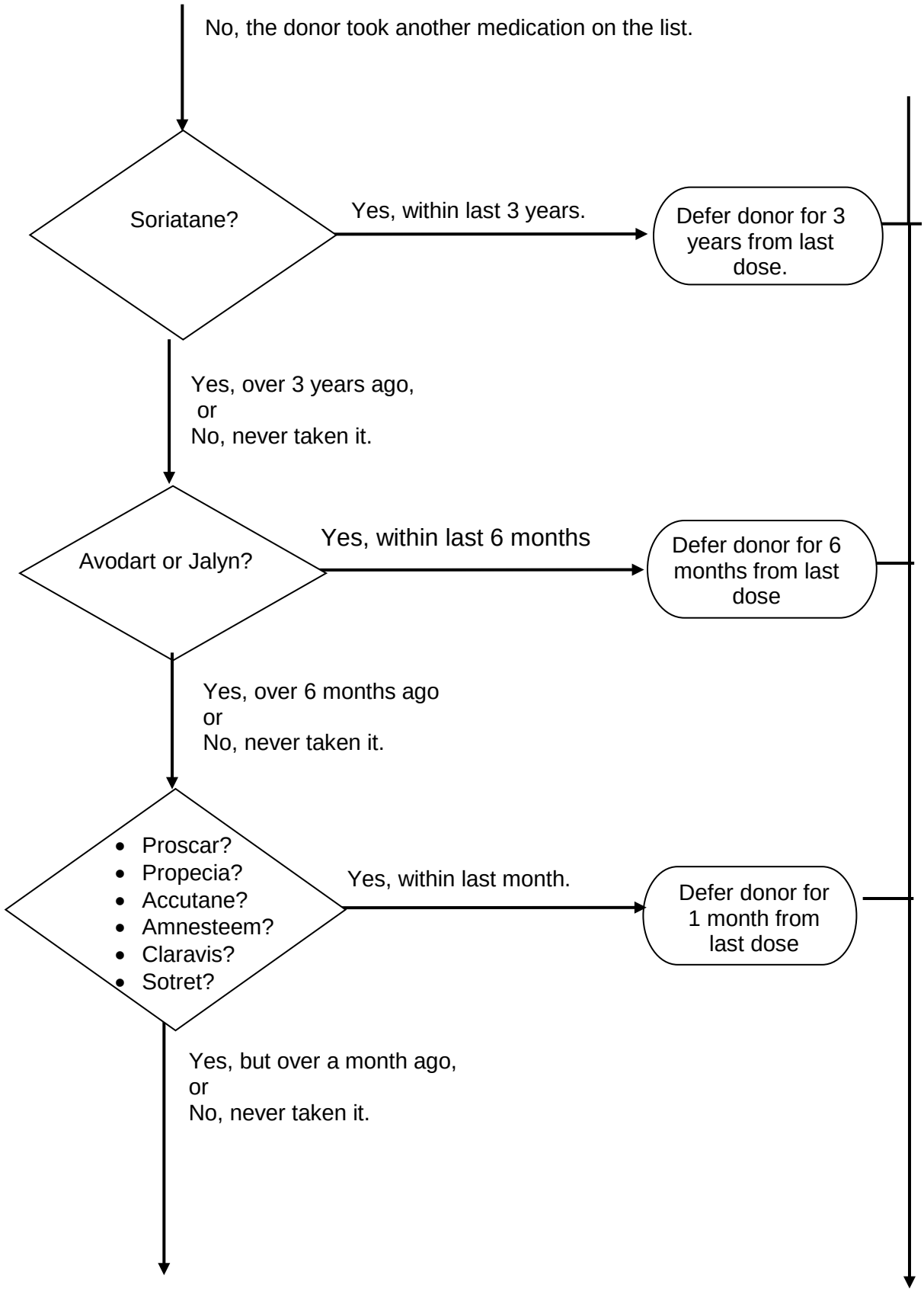
Donor Eligibility: The reason for use of a medication to treat a medical condition must be evaluated (follow company policy).

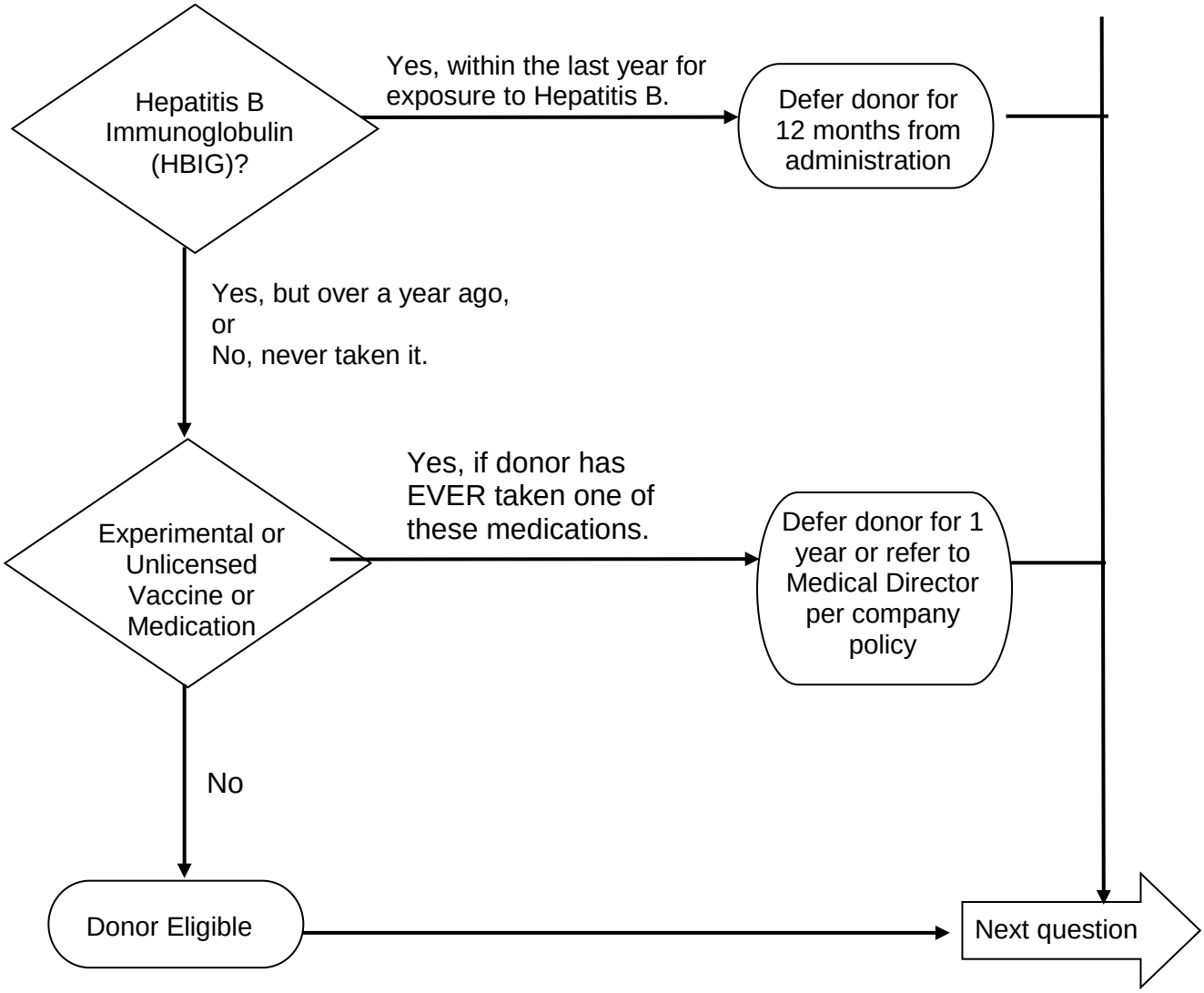


Question #4: Are you now taking or have you ever taken any medications on the medication list?

Donor Eligibility: Donors taking certain designated medications, currently or in the past, must not donate plasma, whole blood or platelets.

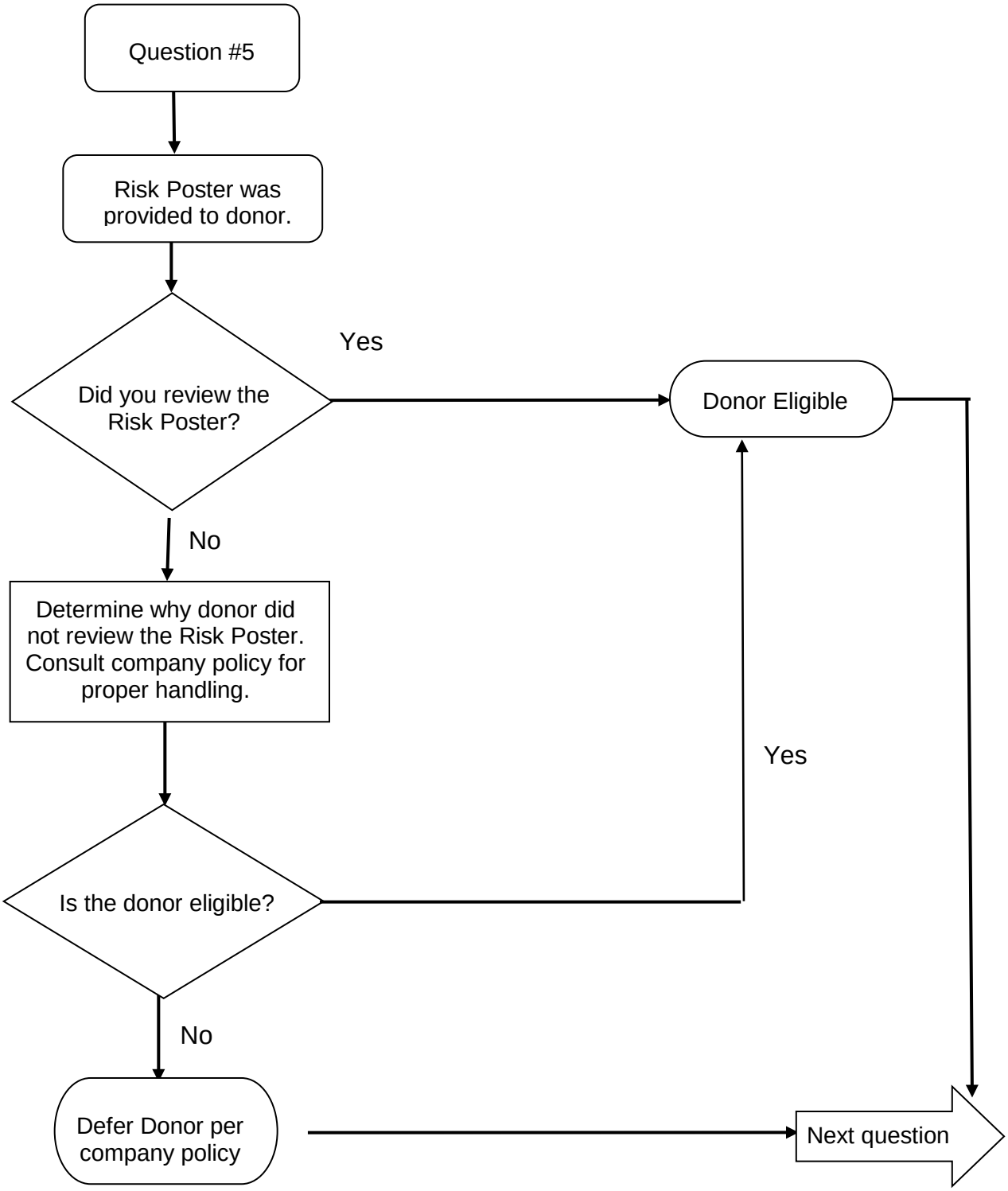



No, the donor took another medication on the list.
Soriatane?
Yes, within last 3 years.
Defer donor for 3 years from last dose.
Yes, over 3 years ago,
or
No, never taken it.
Avodart or Jalyn?
Yes, within last 6 months
Defer donor for 6 months from last dose
Yes, over 6 months ago
or
No, never taken it.
Proscar?
Propecia?
Accutane?
Amnesteem?
Claravis?
Sotret?
Yes, within last month.
Defer donor for 1 month from last dose
Yes, but over a month ago,
or
No, never taken it.


Hepatitis B Immunoglobulin (HBIG)?
Yes, within the last year for exposure to Hepatitis B.
Defer donor for 12 months from administration
Yes, but over a year ago, or No, never taken it.
Experimental or Unlicensed Vaccine or Medication
Yes, if donor has EVER taken one of these medications.
Defer donor for 1 year or refer to Medical Director per company policy
No
Donor Eligible
Next question

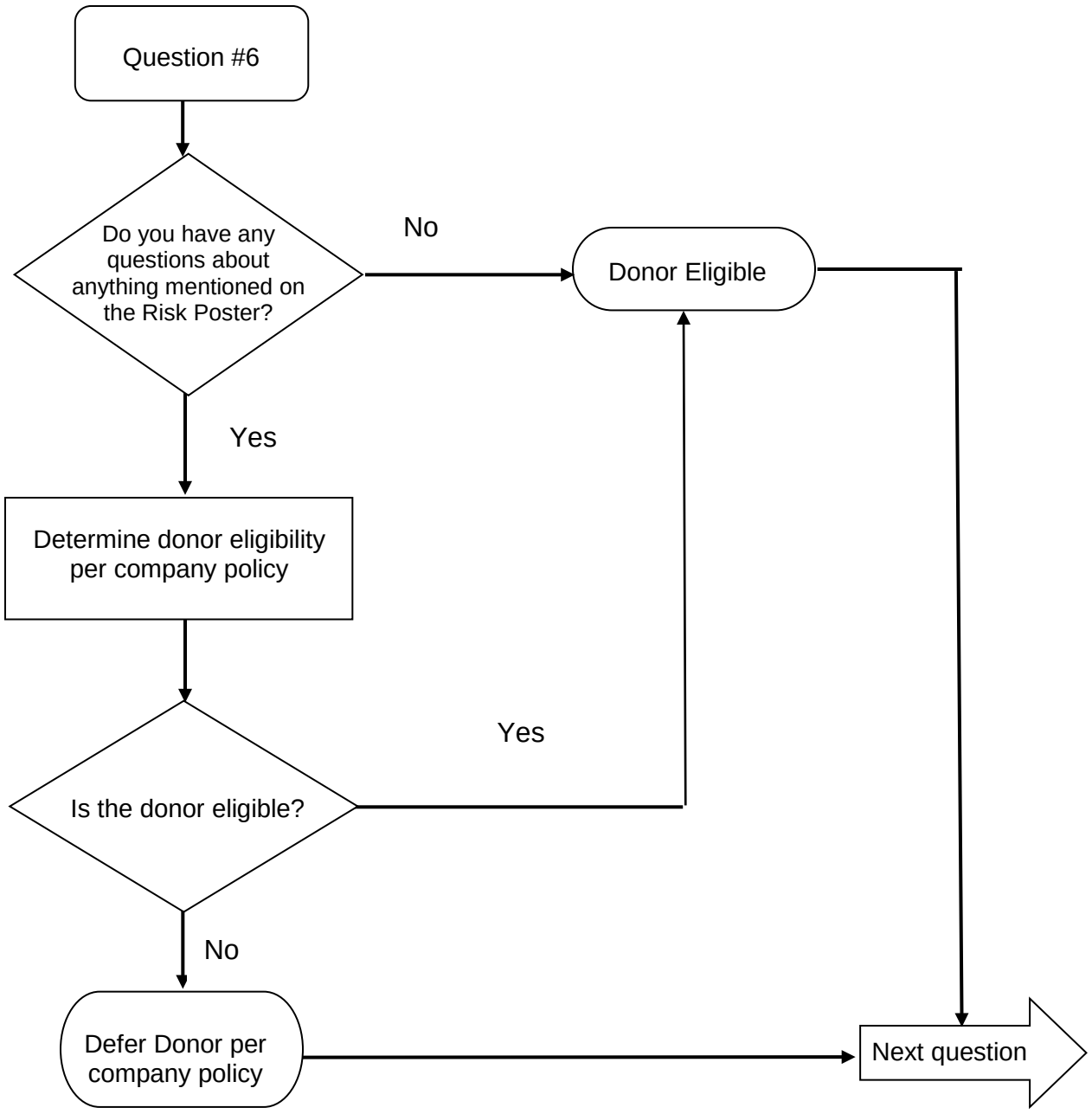
Question #5: Did you review the Risk Poster?

Donor Eligibility: The Risk Poster includes information on risk activities for HIV/AIDS, viral hepatitis, and other infectious diseases that may be transmitted through blood. Therefore, potential plasma donors must read the Risk Poster information provided during the donor interview to determine if they are at risk of transmitting infectious diseases.



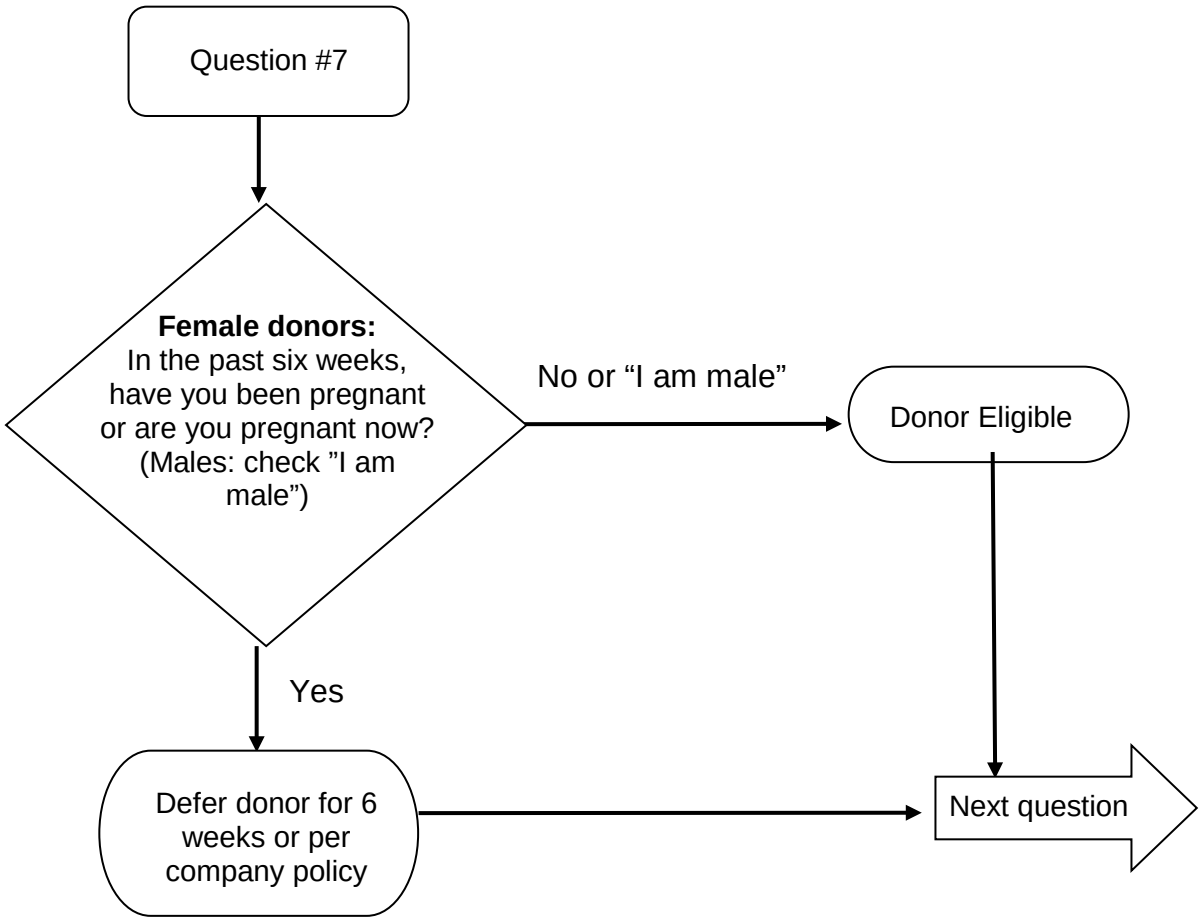
Question #6: Do you have any questions about anything mentioned on the Risk Poster?

Donor Eligibility: The Risk Poster includes information on risk activities for HIV/AIDS, viral hepatitis, and other infectious diseases that may be transmitted through blood. Donors should be encouraged to ask questions if material is not understood. For donor deferral follow company policy.



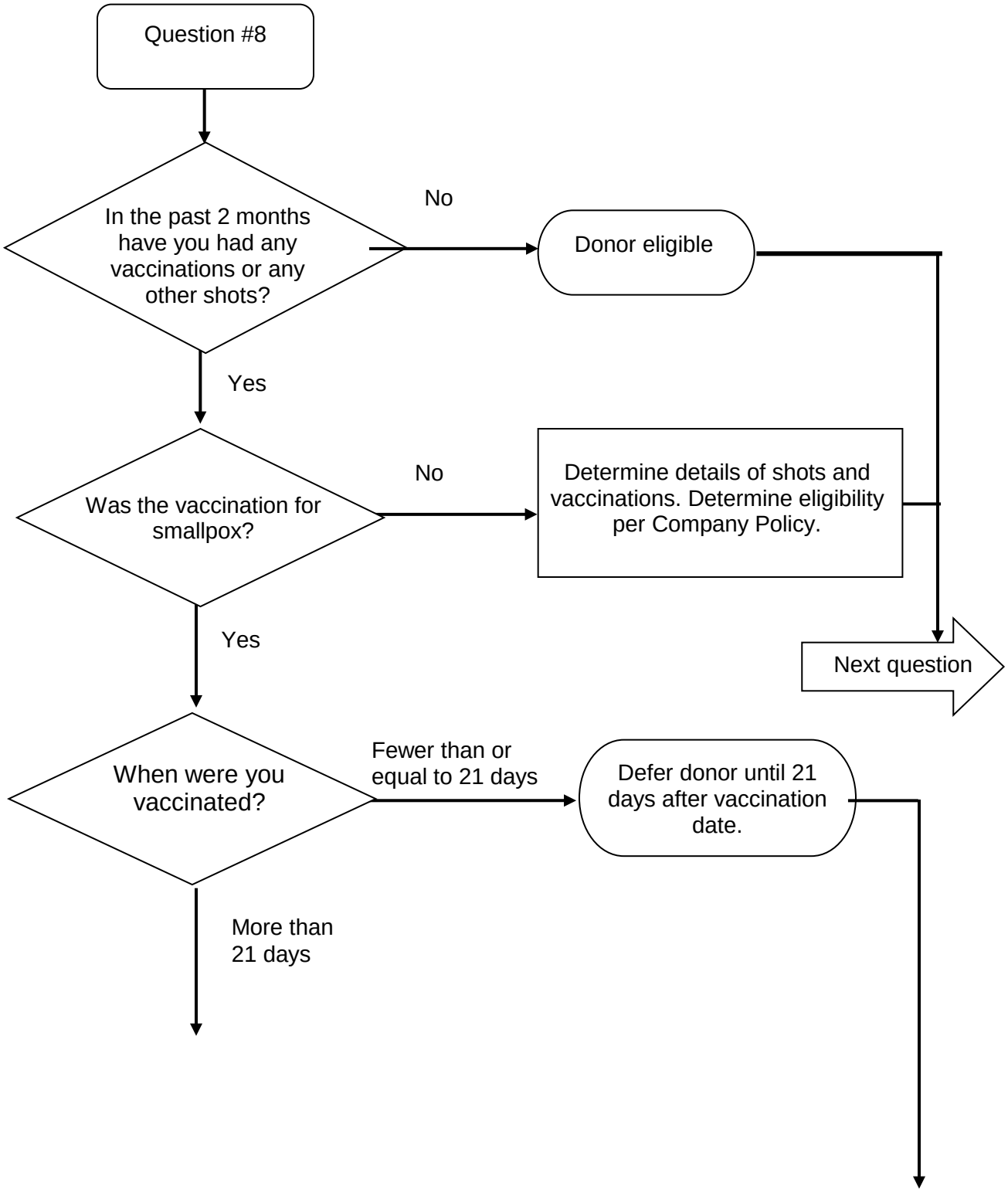
Question #7: Female donors: In the past six weeks, have you been pregnant or are you pregnant now? (Males: check ”I am male”)

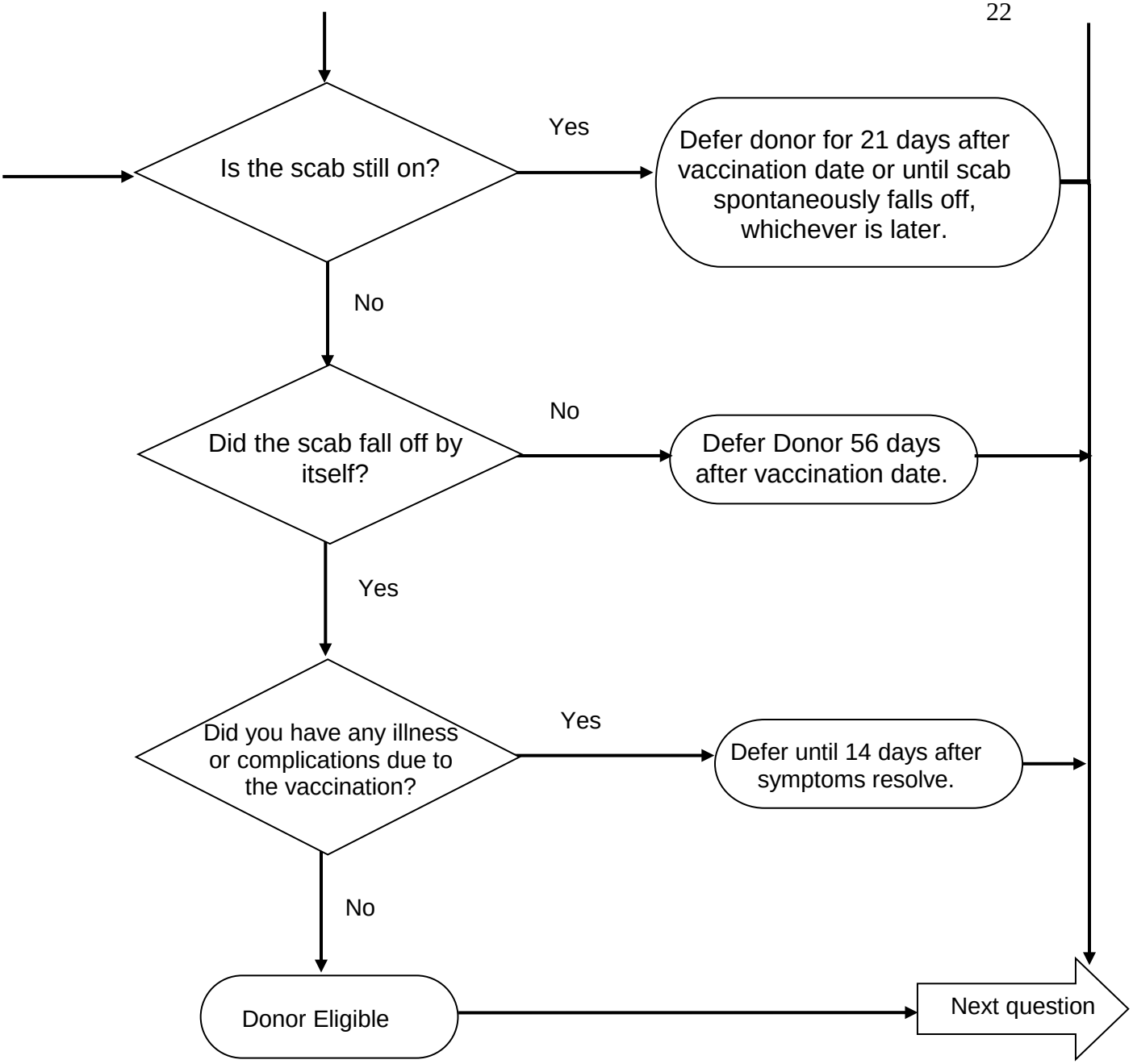
Donor Eligibility: A female with a known pregnancy or who has been pregnant in the last six weeks should not donate blood or plasma.



Question #8: In the past 2 months have you had any vaccinations or other shots?

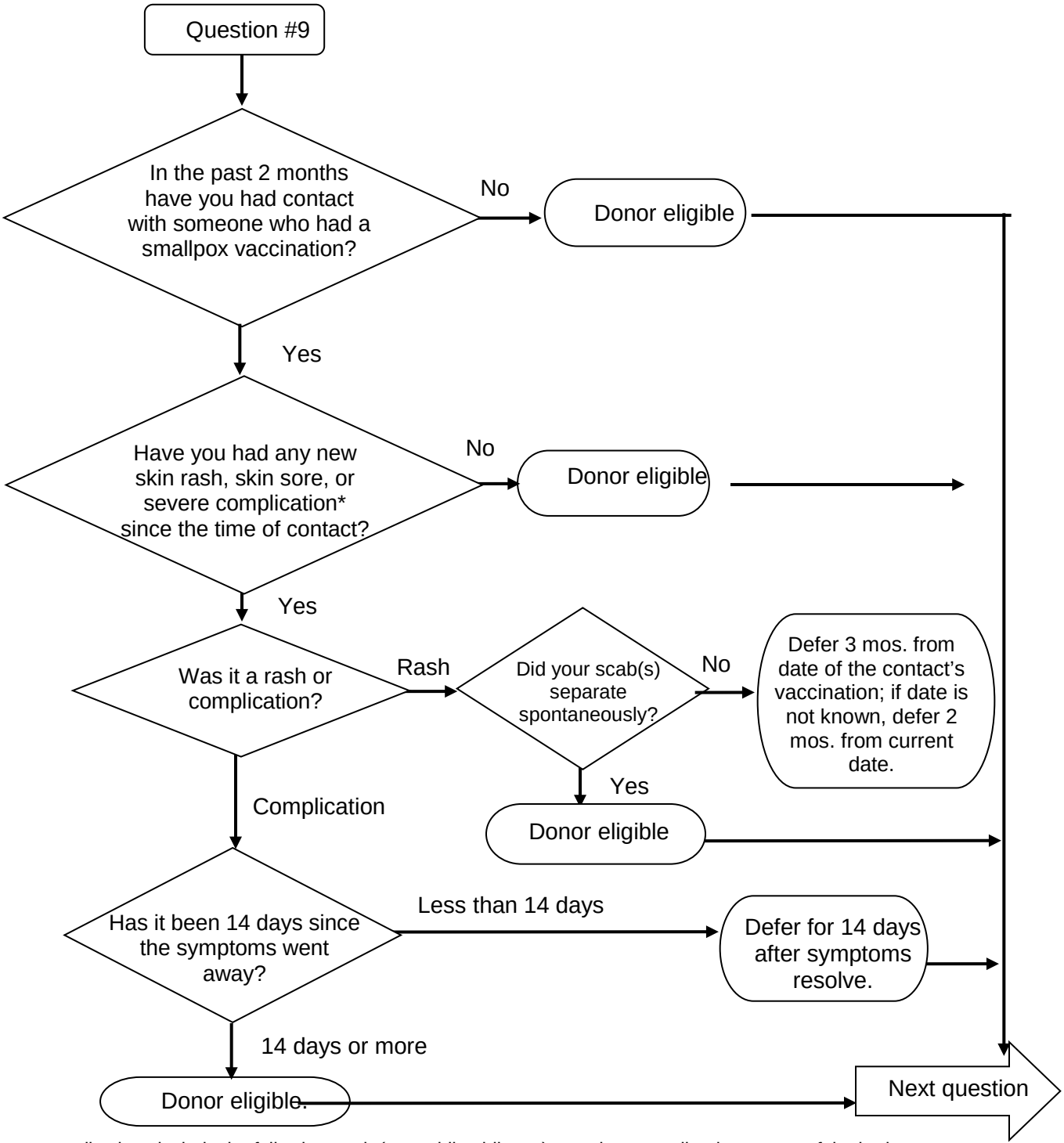
Donor Eligibility: Certain vaccinations may contain a live virus. A donor who has been exposed to a live virus via vaccination should not serve as a donor. For other shots, consult company policy to determine eligibility.




Is the scab still on?
Yes
Defer donor for 21 days after vaccination date or until scab spontaneously falls off, whichever is later.
No
Did the scab fall off by itself?
No
Defer Donor 56 days after vaccination date.
Yes
Did you have any illness or complications due to the vaccination?
Yes
Defer until 14 days after symptoms resolve.
No
Donor Eligible
Next question

Question #9: In the past 2 months have you had contact with someone who had a smallpox vaccination?

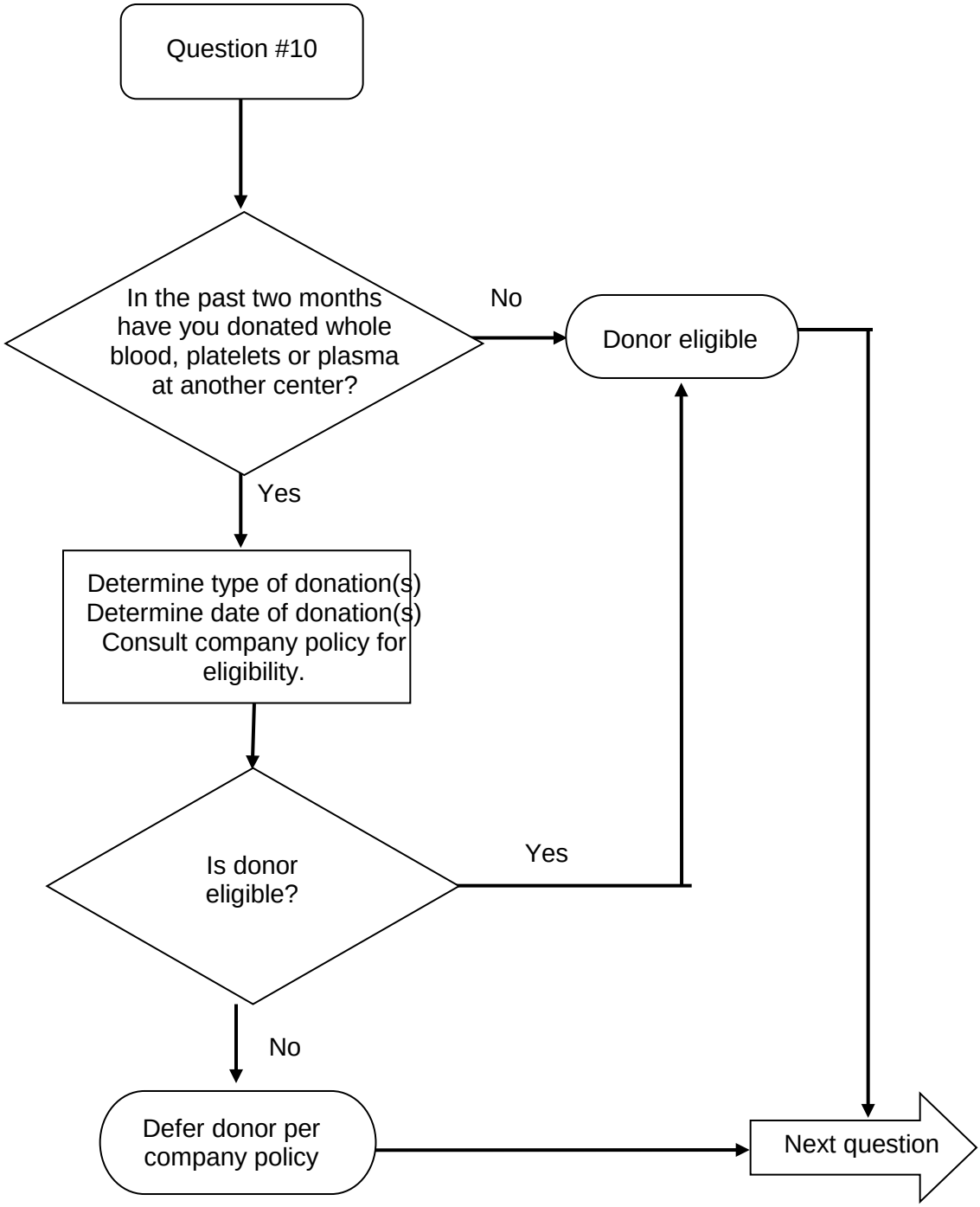
Donor Eligibility: Certain vaccinations may contain a live virus. A donor who has been exposed to a live virus via vaccination should not serve as a donor. For other shots, consult company policy to determine eligibility.



*Severe complications include the following: rash (resembling blisters) covering a small or large area of the body; necrosis (tissue death) in the area of exposure; encephalitis (inflammation of the brain); infection of the cornea (eye) and localized or systemic skin reaction in someone with eczema or other chronic skin condition.

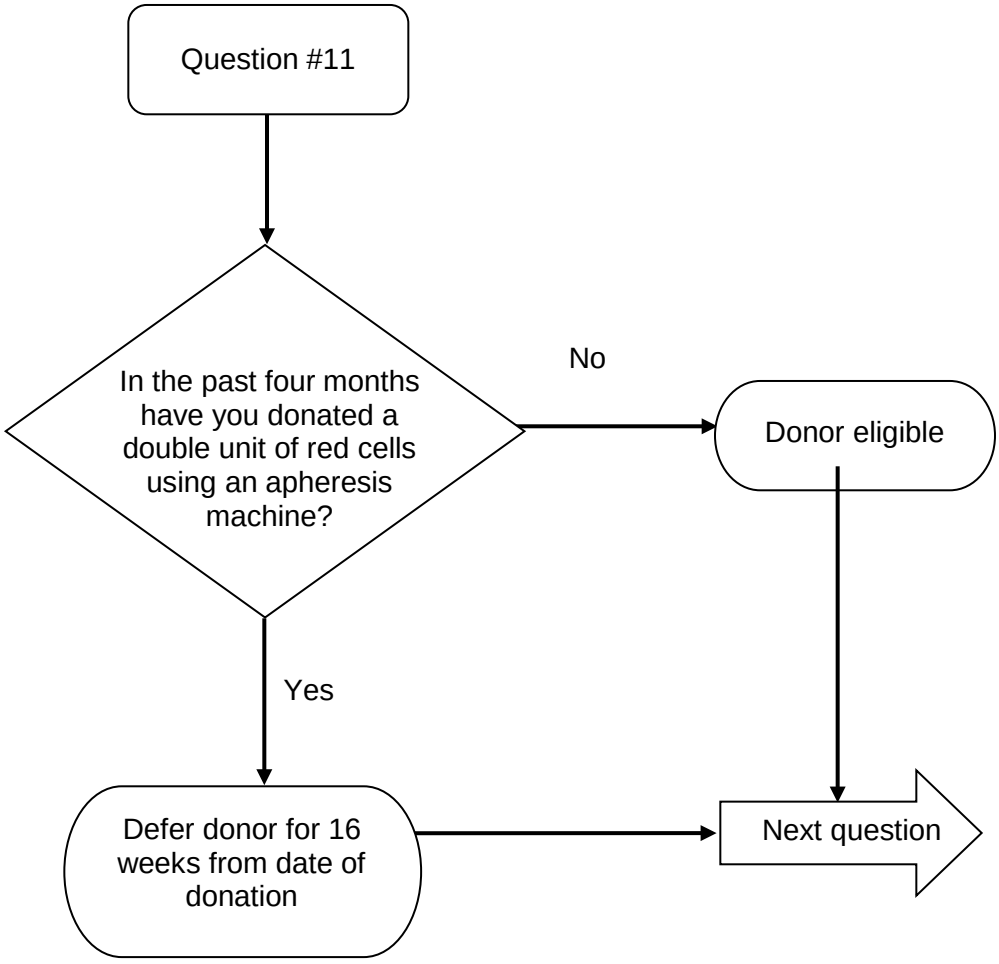
Question #10: In the past two months have you donated whole blood, platelets or plasma at another center?

Donor Eligibility: A donor who has donated a unit of whole blood should not donate blood or plasma for a period of 8 weeks. A donor who has donated platelets (cellular component that aids in clotting blood) or plasma by apheresis should not donate more than two times in a seven-day period at intervals of no less than two days apart. For other blood components or conditions of collection (e.g., less than a unit of whole blood), the donor should be deferred for the period established in the company policy.



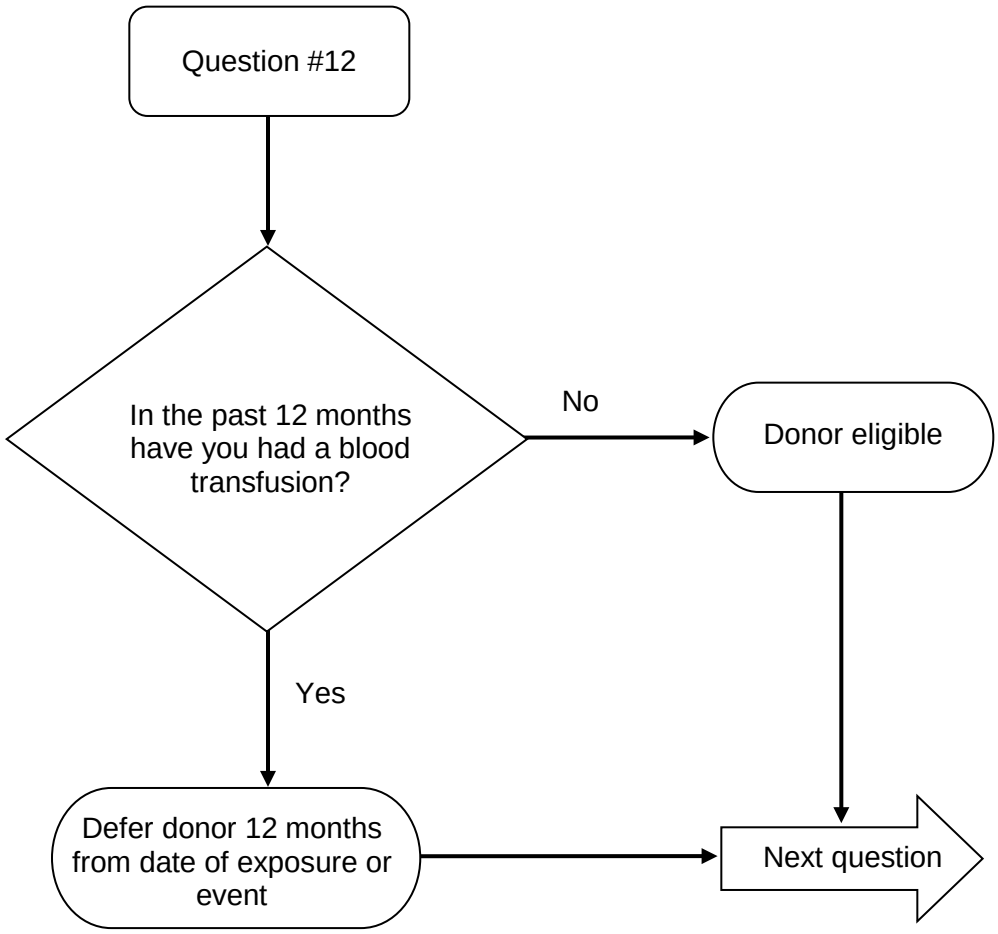
Question #11: In the past four months have you donated a double unit of red cells using an apheresis machine?

Donor Eligibility: A donor who has donated a double unit of red cells *(the volume of red cells in two units of blood)* by apheresis should not donate blood or plasma for a period of four months *(*16 weeks). The donor is attached to a machine similar to the one used for plasma donation. However, the donor's plasma is given back to the donor, and the blood collection facility keeps the two units of red blood cells. The 4-month deferral is needed for the donor to replace the red cells donated.



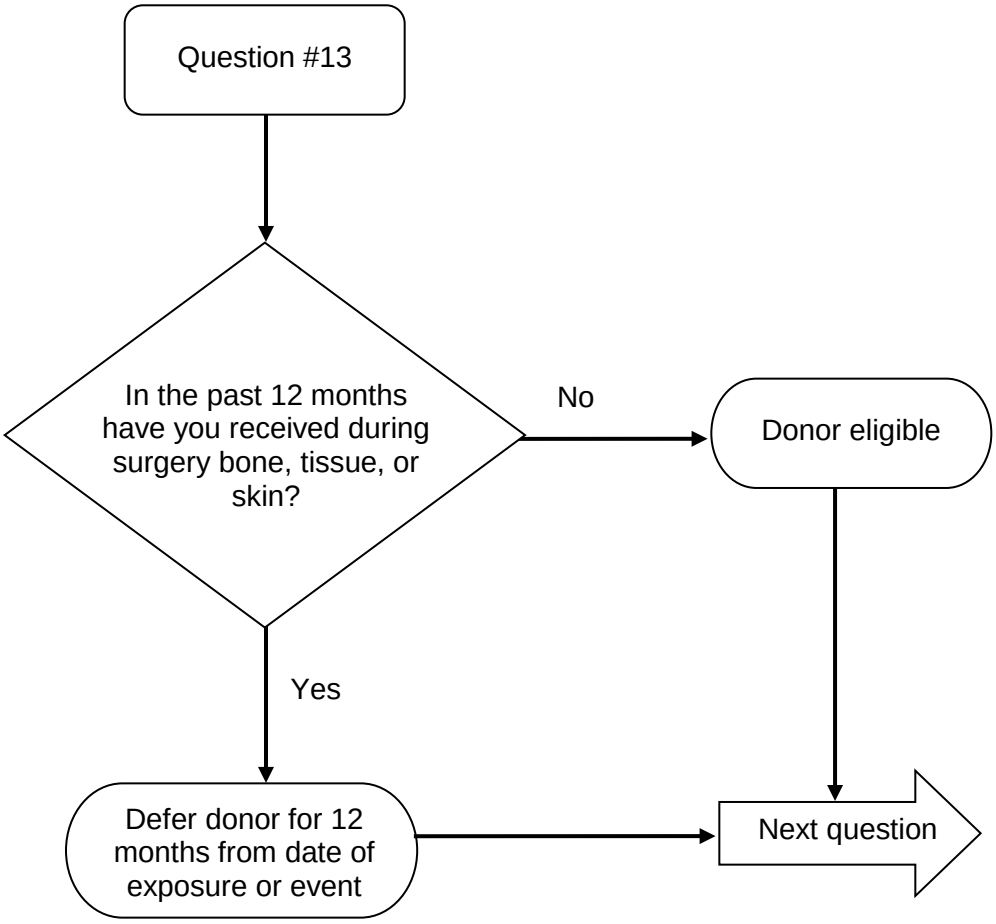
Question #12: In the past 12 months have you had a blood transfusion?

Donor Eligibility: A donor who has received a transfusion of blood, platelets, plasma or other blood component should not donate blood or plasma for 12 months following the transfusion, due to possible transmissibility of infectious disease.



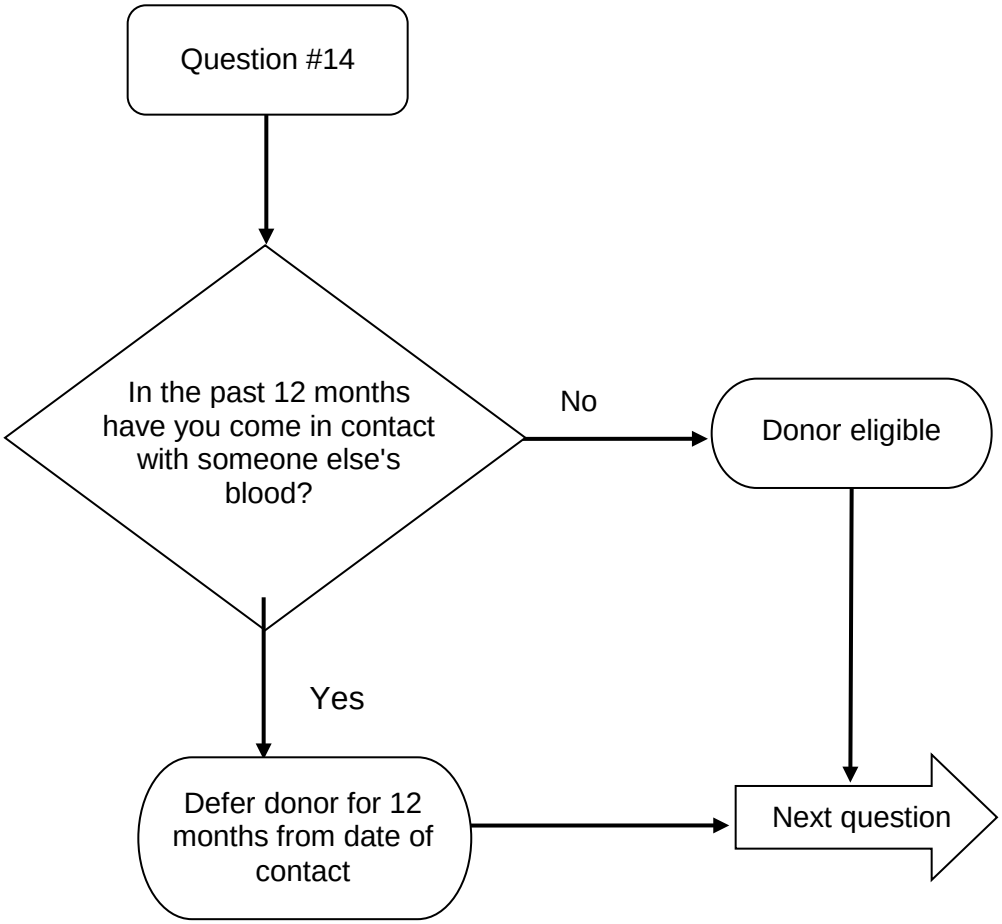
Question #13: In the past 12 months have you received during surgery bone, tissue, or skin?

Donor Eligibility: A donor who has been exposed to tissues during surgery should not donate blood or plasma for 12 months following exposure, due to possible transmissibility of infectious disease.



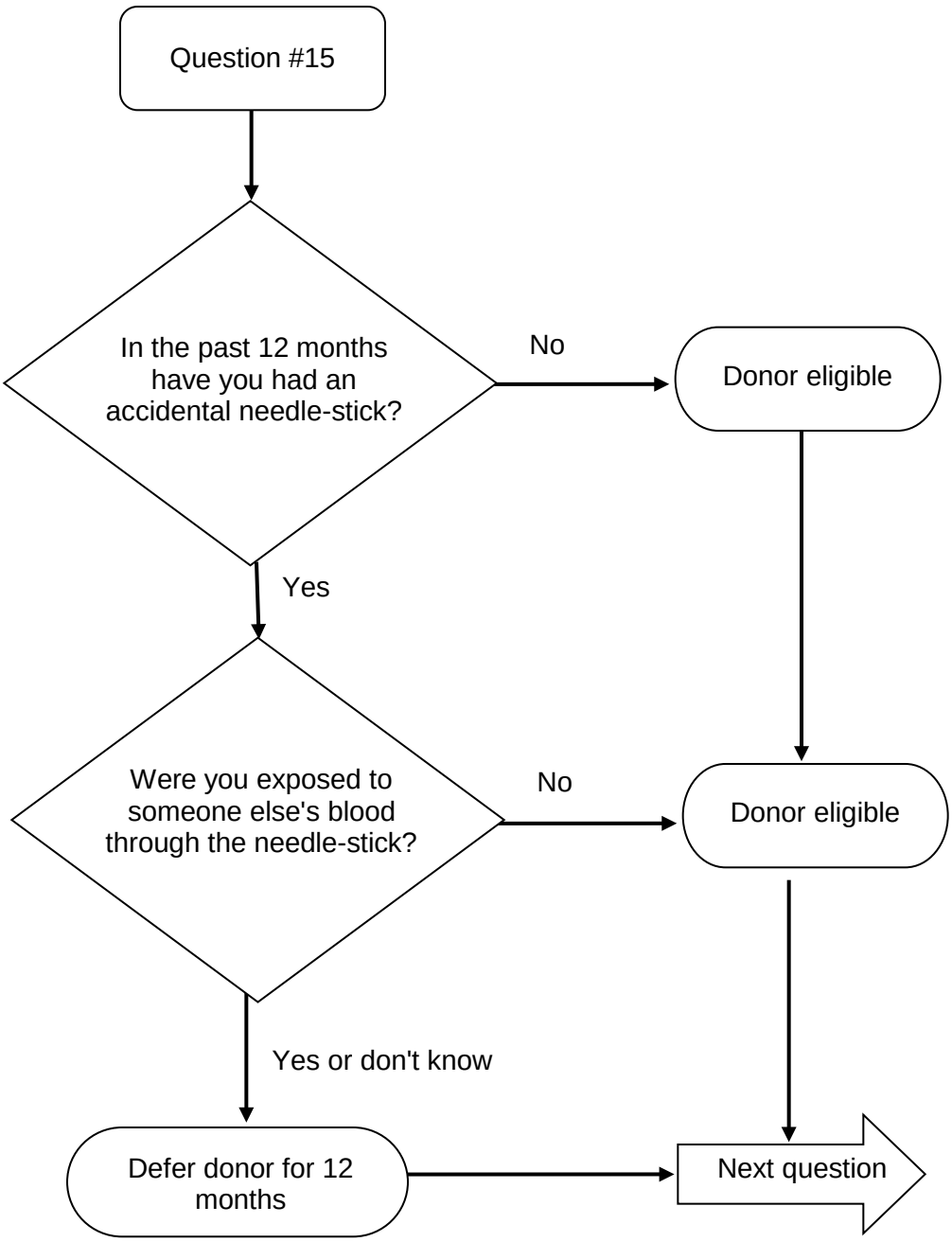
Question #14: In the past 12 months have you come in contact with someone else's blood?

Donor Eligibility: Persons who have had one of the following during the preceding 12 months: 1) contact of an open wound, non-intact skin or mucous membrane with the blood of a person, or 2) a needle-stick or other sharps injury from an instrument that has been used on a person, are deferred for 12 months from the date of exposure. Infectious diseases may be spread through contact with blood.



Question #15: In the past 12 months have you had an accidental needle-stick?

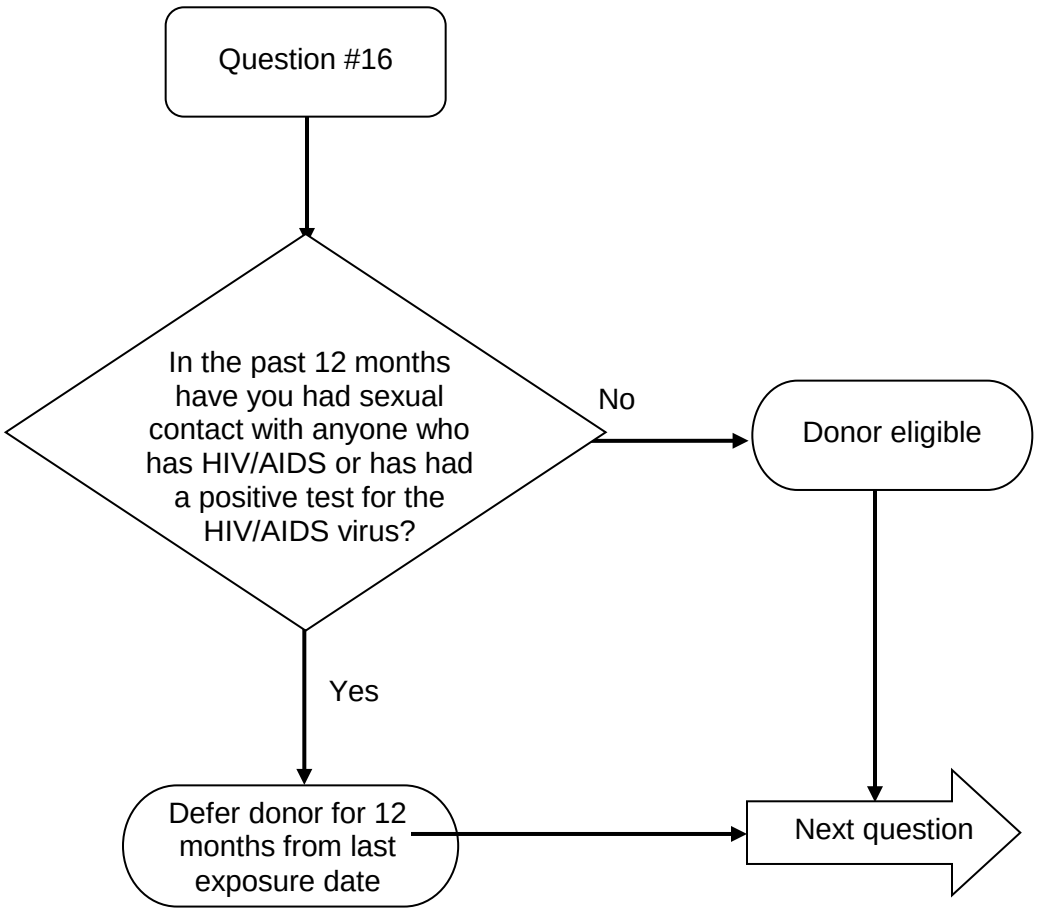
Donor Eligibility: A donor who has been exposed to someone else's blood through a needle-stick should not donate blood or plasma for 12 months following exposure, due to possible transmissibility of infectious disease.



Question #16: In the past 12 months have you had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?

Donor Eligibility: Persons who have had sexual contact with persons with clinical or laboratory evidence of HIV infection are deferred for 12 months from the date of last contact. HIV may be transmitted through sexual contact with an infected person.

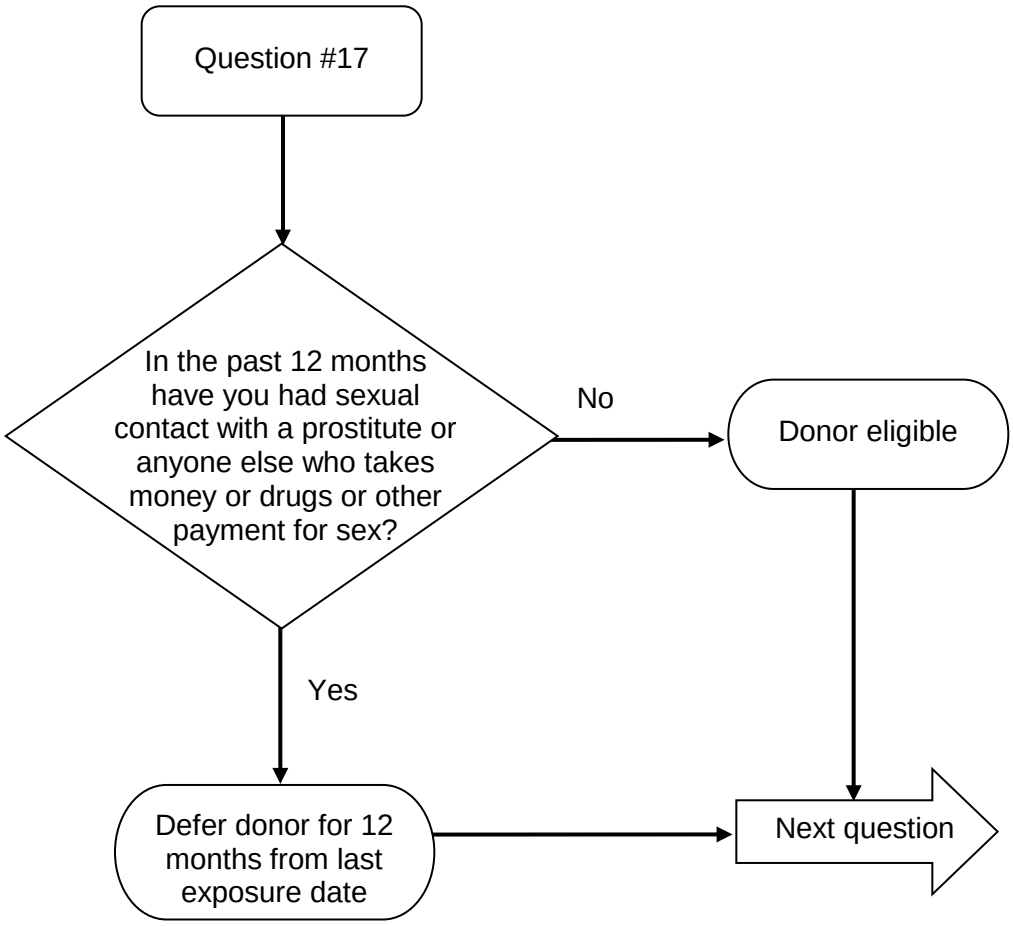
Note: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.



Question #17: In the past 12 months have you had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?

Donor Eligibility: Persons who have given money or drugs in exchange for sex (sexual contact) are deferred for 12 months from the date of the last sexual contact. HIV and other diseases may be transmitted through sexual contact.

Note: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.

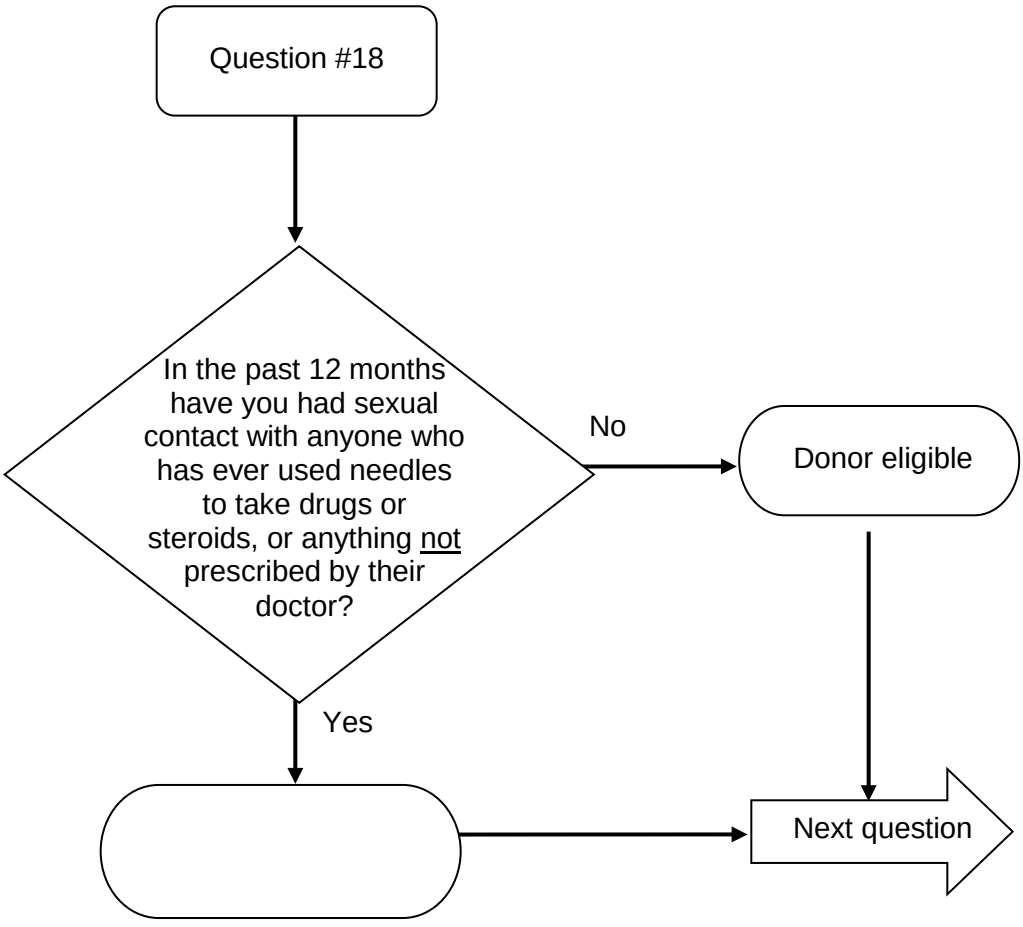


Question #18: In the past 12 months have you had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?

Donor Eligibility: Persons who have had sexual contact with persons who, in the past or present, have used needles to take drugs, steroids, or anything not prescribed by their doctor are deferred for 12 months from the date of the last sexual contact. HIV and other diseases may be transmitted through sexual contact.

Note 1: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.

Note 2: The phrase "use of a needle" includes intravenous use, "skin popping" (injection under the skin), "mainlining" (arterial injection) and any other use of a needle to administer drugs, steroids or anything else not prescribed by their doctor.

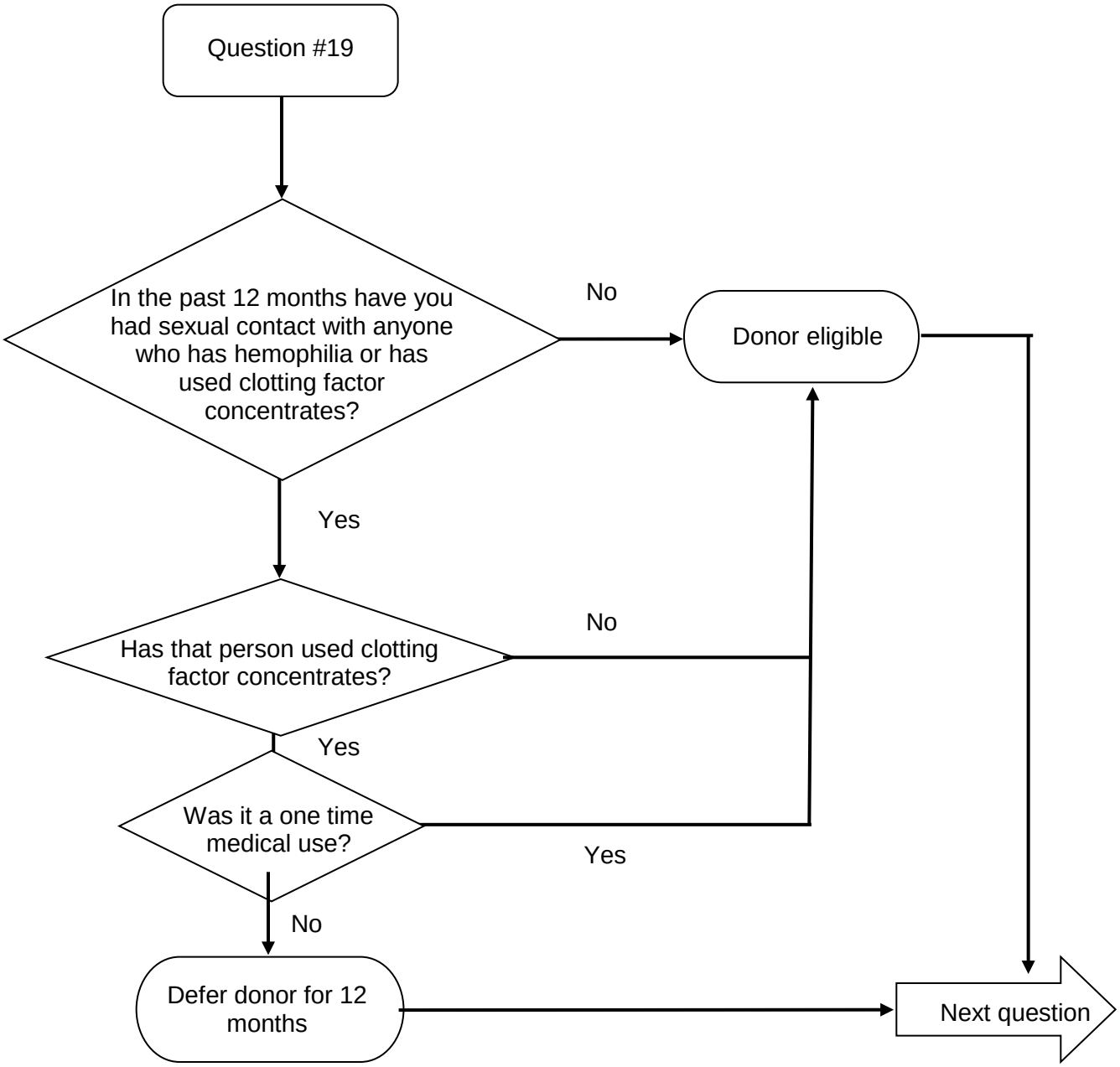


Question #19: In the past 12 months have you had sexual contact with anyone who has hemophilia or has used clotting factor concentrates?

Donor Eligibility: Persons who have had sexual contact with any person who has received clotting factor concentrates is deferred for 12 months. HIV and other diseases may be transmitted through sexual contact.

Note: Some hemophiliacs are not treated with clotting factor concentrates.

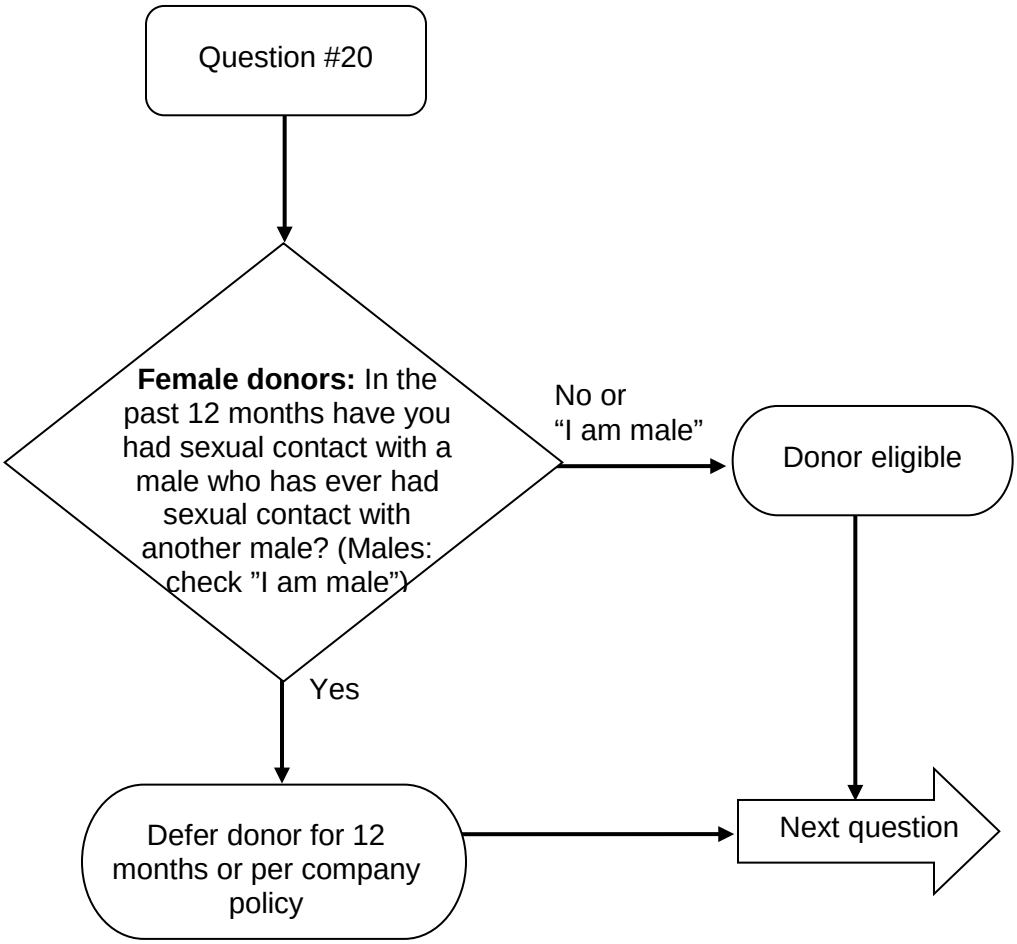
Note: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.



Question #20: Female donors: In the past 12 months have you had sexual contact with a male who has ever had sexual contact with another male? (Males: check ”I am male”)

Donor Eligibility: Women who have had sexual contact with men who have had sexual contact with another man even one time since 1977 are deferred for 12 months from the date of last sexual contact. HIV and other diseases may be transmitted through sexual contact.

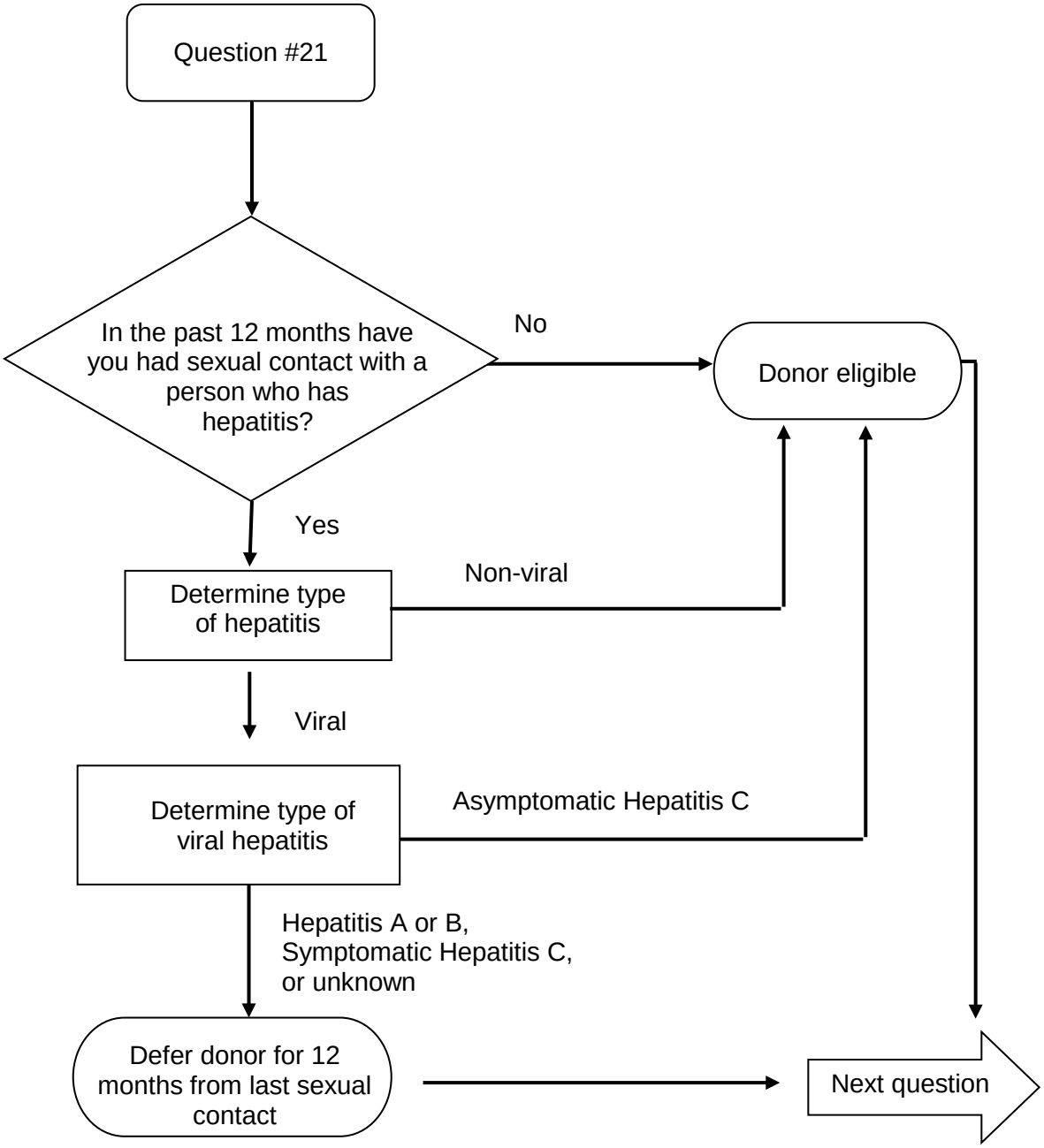
Note: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.



Question #21: In the past 12 months have you had sexual contact with a person who has hepatitis?

Donor Eligibility: Persons who report having had sexual contact with a person who has hepatitis are to be deferred for 12 months from the time of last exposure. Hepatitis, particularly hepatitis B, may be spread through sexual contact.

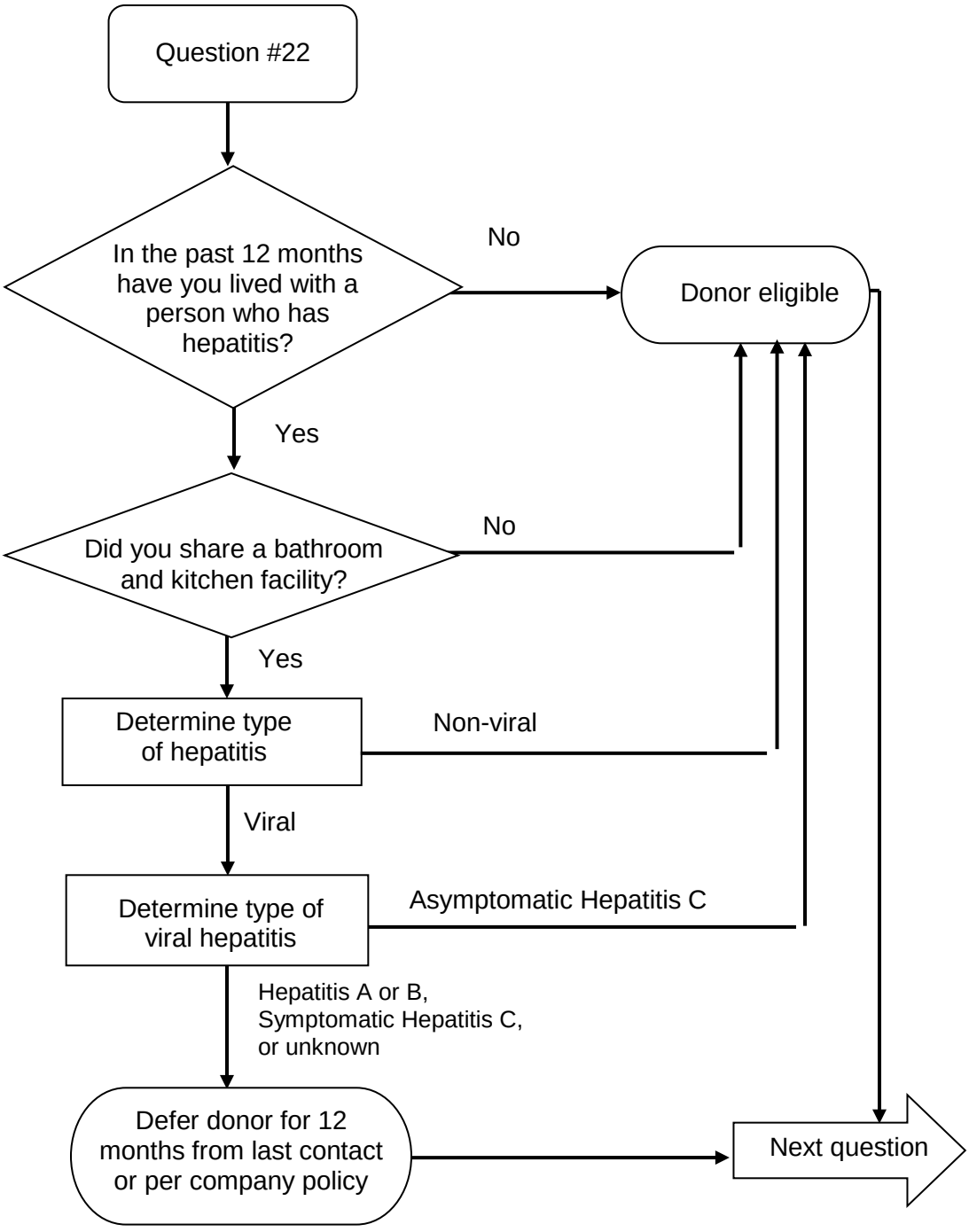
Note: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.



Question #22: In the past 12 months have you lived with a person who has hepatitis?

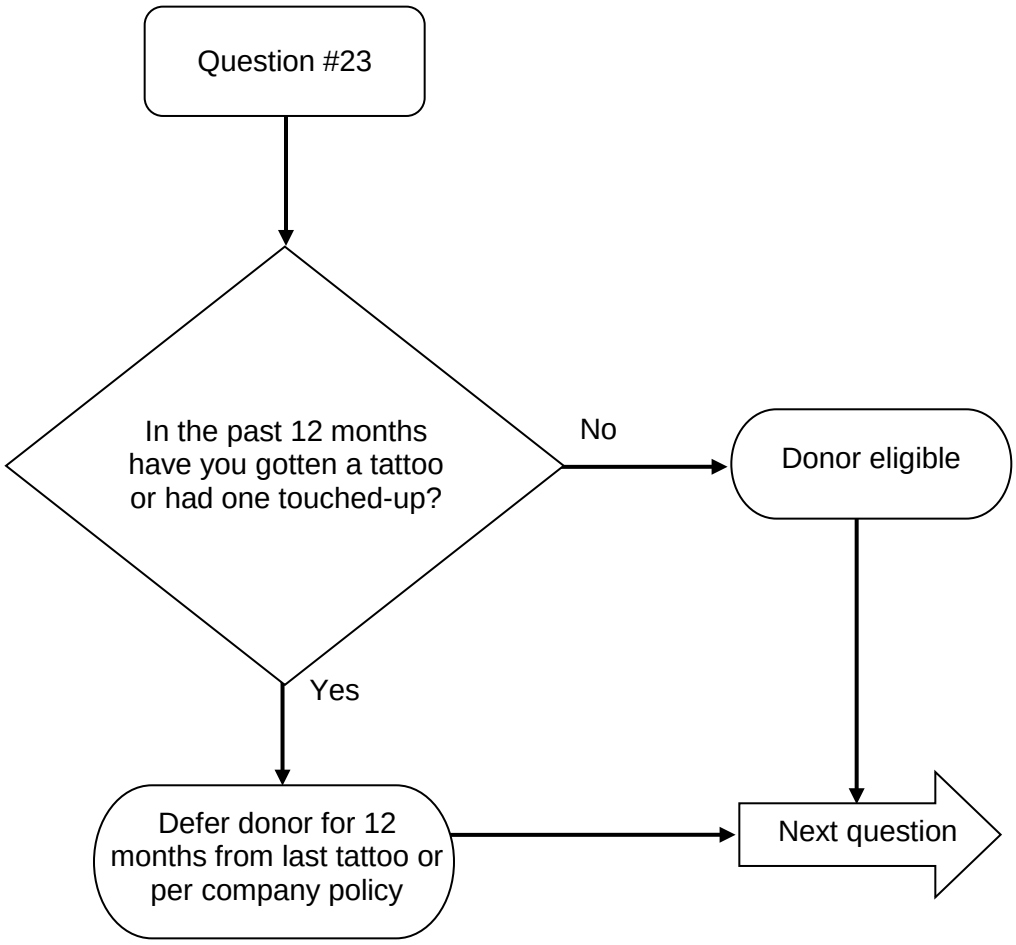
Donor Eligibility: Persons who have lived with a person who has hepatitis are deferred 12 months from the date of last contact. Hepatitis, particularly Hepatitis A and B, may be spread through saliva.

Note: "Lived with" means residing at the same address and sharing bathroom and kitchen facilities.



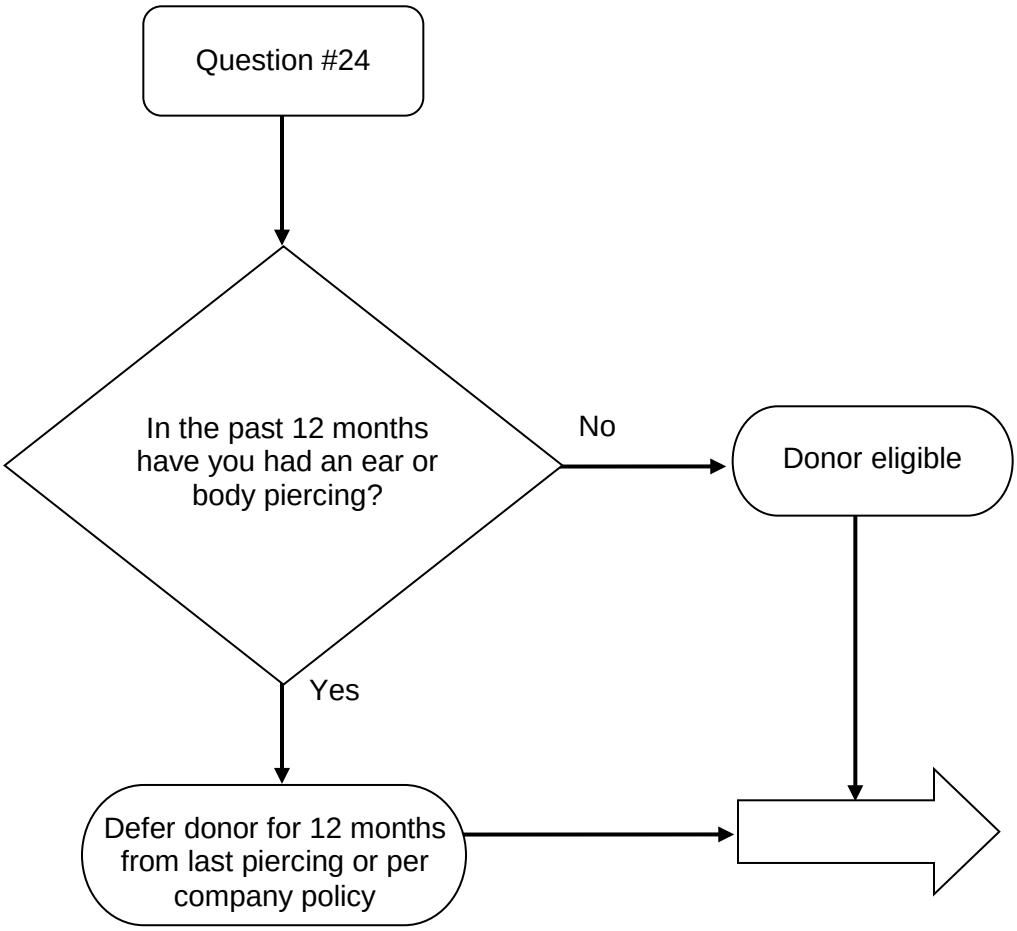
Question #23: In the past 12 months have you gotten a tattoo or had one touched-up?

Donor Eligibility: Persons who have received a tattoo in the previous 12 months are deferred for 12 months from the date of the tattoo application because there may be a risk of transmission of infectious diseases. If tattoos have been applied using sterile needles and non-reused ink (such as in establishments licensed by a state or credentialed by a responsible certifying body), donors may be acceptable for donation (follow company policy).



Question #24: In the past 12 months have you had an ear or body piercing?

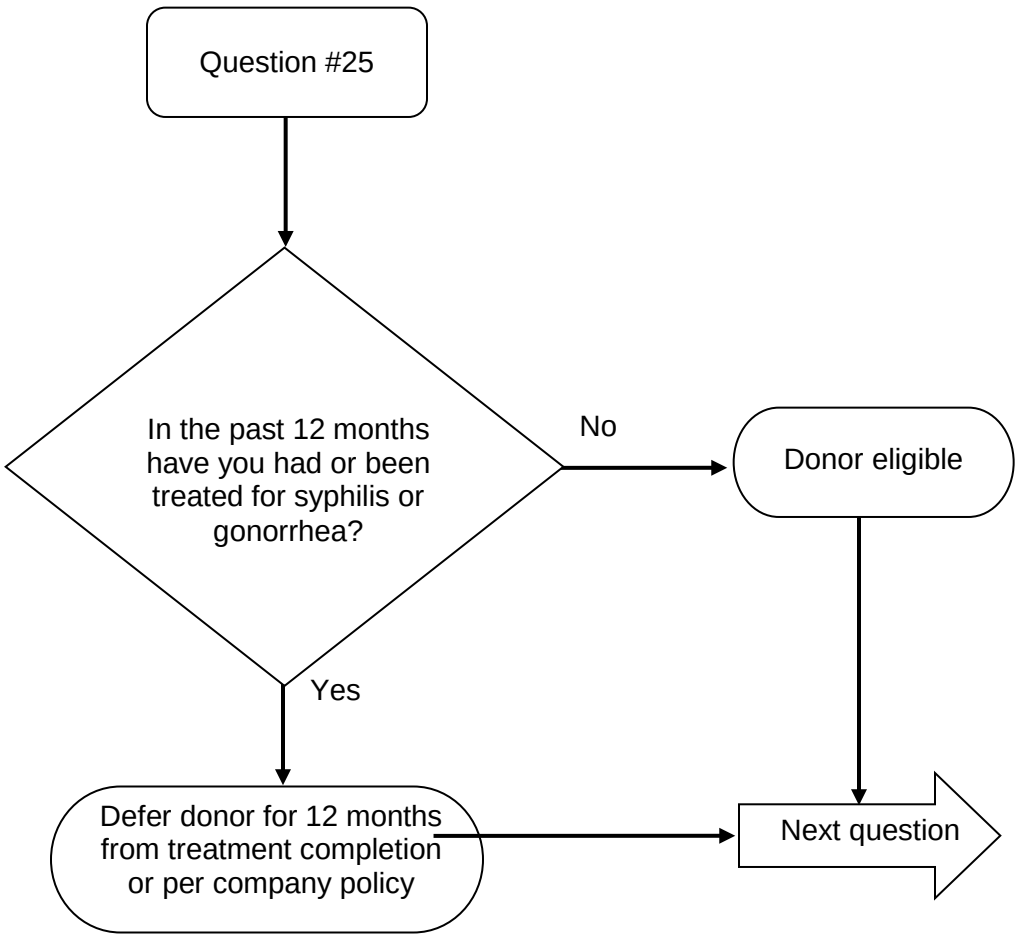
Donor Eligibility: Persons who have had ear or body piercing during the previous 12 months are usually deferred for 12 months from the date of procedure. Unless ear or body piercing have been done using single-use equipment, there may be a risk of transmission of infectious diseases.



Question #25: In the past 12 months have you had or been treated for syphilis or gonorrhea?

Donor Eligibility: Persons who have had syphilis or gonorrhea or treatment for either are deferred for a minimum of 12 months from the date that treatment is completed.

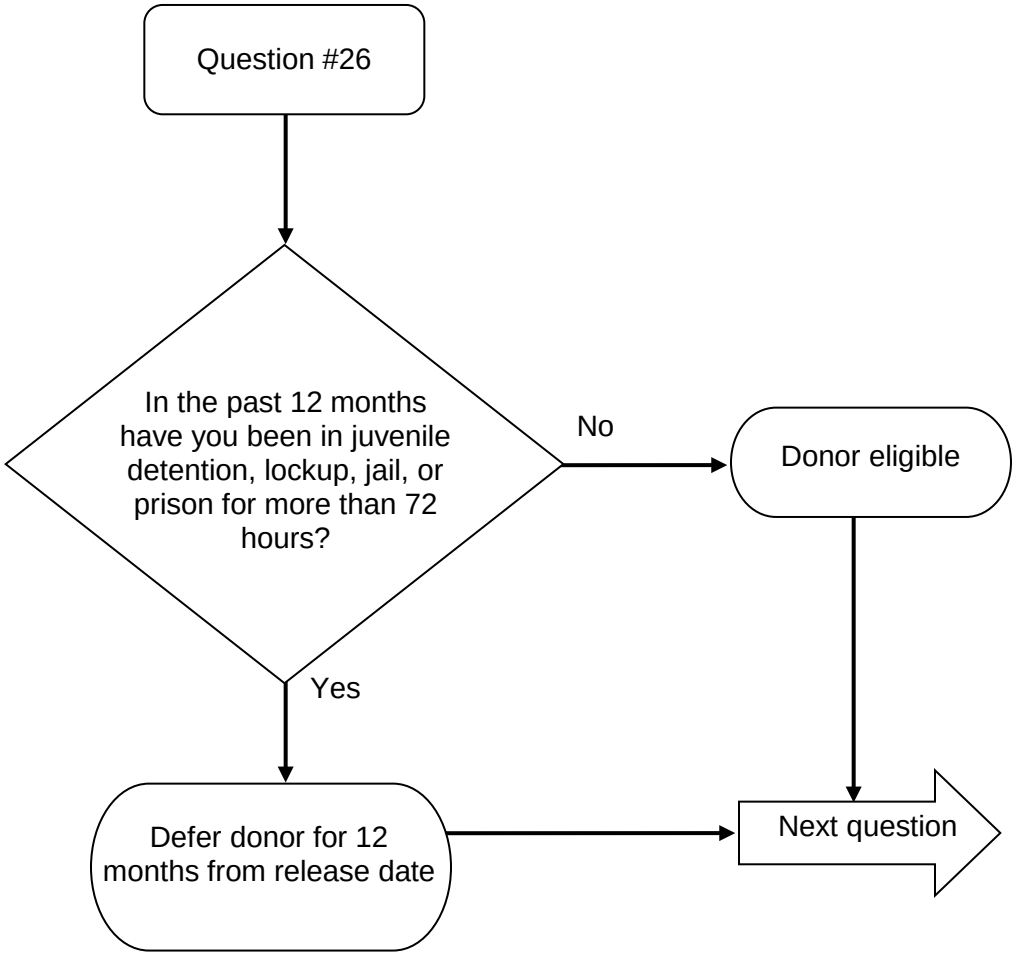
Note: Should a donor volunteer that they were tested and found positive for either syphilis or gonorrhea, deferral is indicated.



Question #26: In the past 12 months have you been in juvenile detention, lockup, jail, or prison for more than 72 hours?

Donor Eligibility: Persons who have been detained or incarcerated in a facility (juvenile detention, lockup, jail, or prison) for more than 72 consecutive hours (three days) are deferred for 12 months from the date of occurrence. These persons are at higher risk for exposure to infectious diseases.

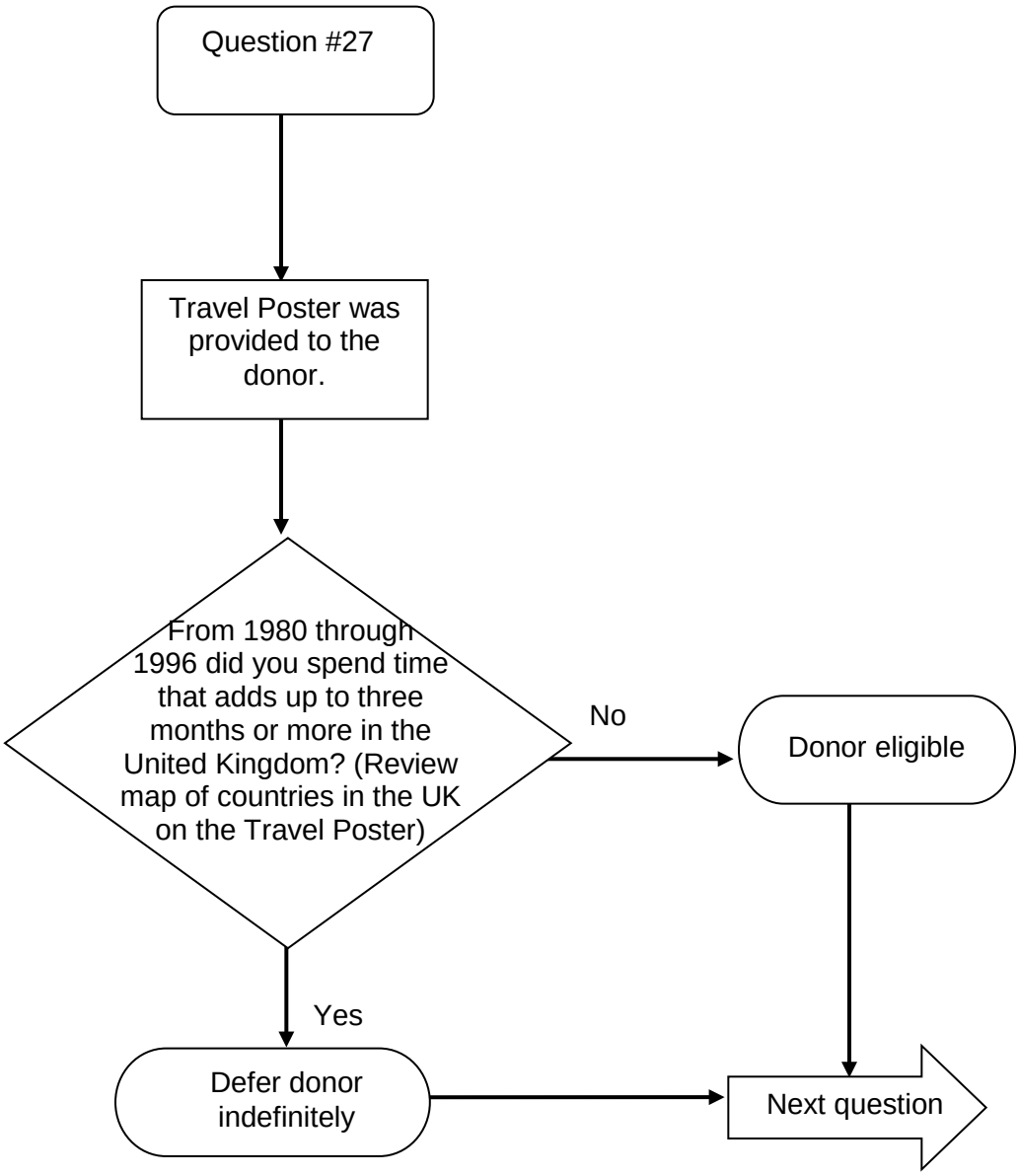
Note: The reason for incarceration (e.g. white-collar crimes) does not change the deferral.



Question #27: From 1980 through 1996 did you spend time that adds up to three months or more in the United Kingdom? (Review map of UK countries on the Travel Poster)

Donor Eligibility: Donors who have spent time that adds up to three months or more in the United Kingdom from 1980 through 1996 are indefinitely deferred. Donors may be at risk of developing vCJD from eating beef from the UK (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or Falkland Islands.). There is a risk of transmitting vCJD through blood transfusion.

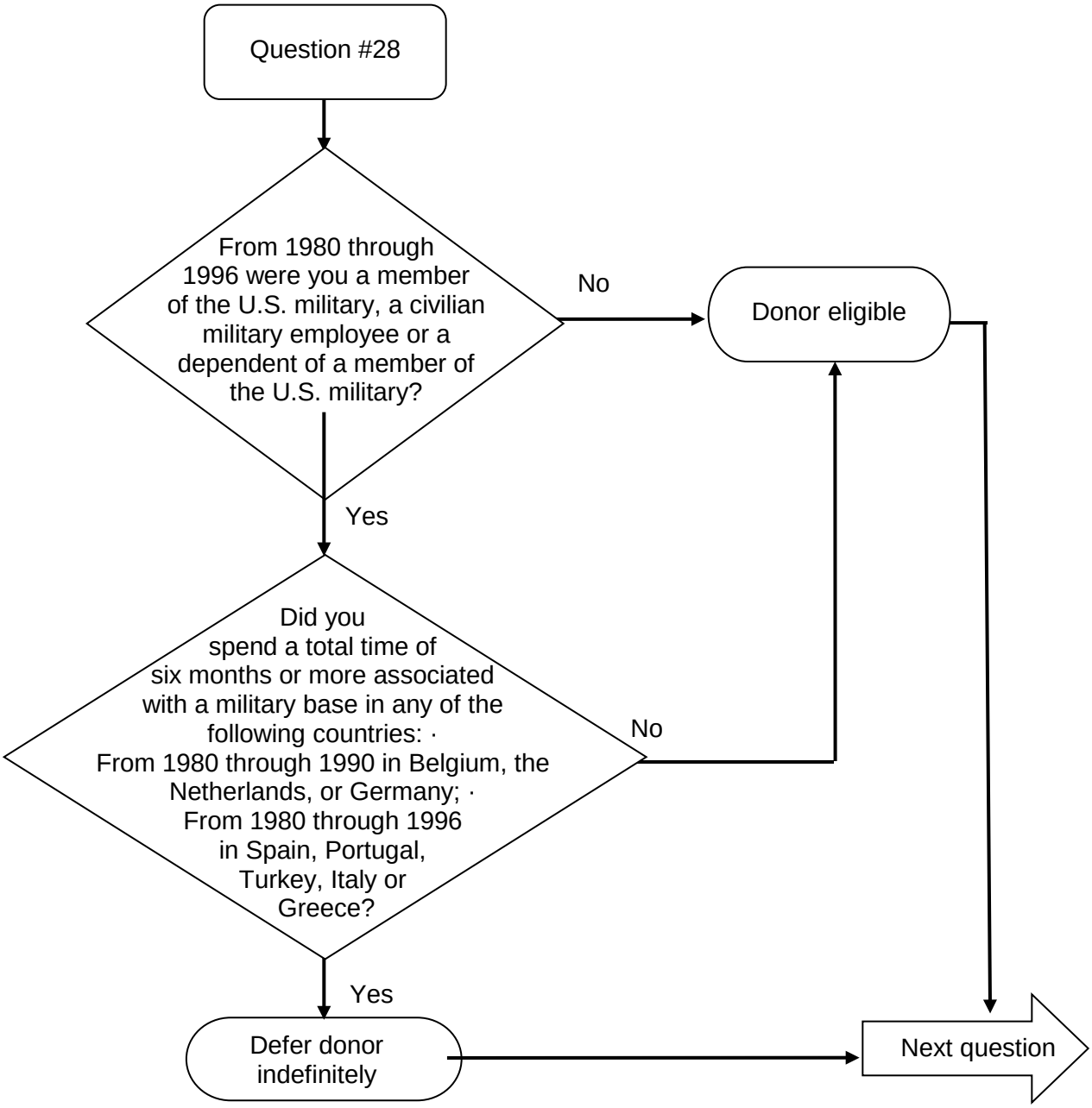
Note: When responding to question, donor should be presented with Travel Poster. The Travel Poster should be available to donor for subsequent questions related to travel.



Question #28: From 1980 through 1996 were you a member of the U.S. military, a civilian military employee or a dependent of a member of the U.S. military?

Donor Eligibility: Members of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military are indefinitely deferred if they spent a total of six months or more associated with a military base in any of the following countries: From 1980 through 1990 in Belgium, the Netherlands, or Germany; From 1980 through 1996 in Spain, Portugal, Turkey, Italy or Greece. Much of the beef supplied to U.S. military bases during these time periods came from the United Kingdom (U.K.). As a result, these U.S. military personnel may be at risk of developing vCJD and transmitting vCJD through blood and plasma.

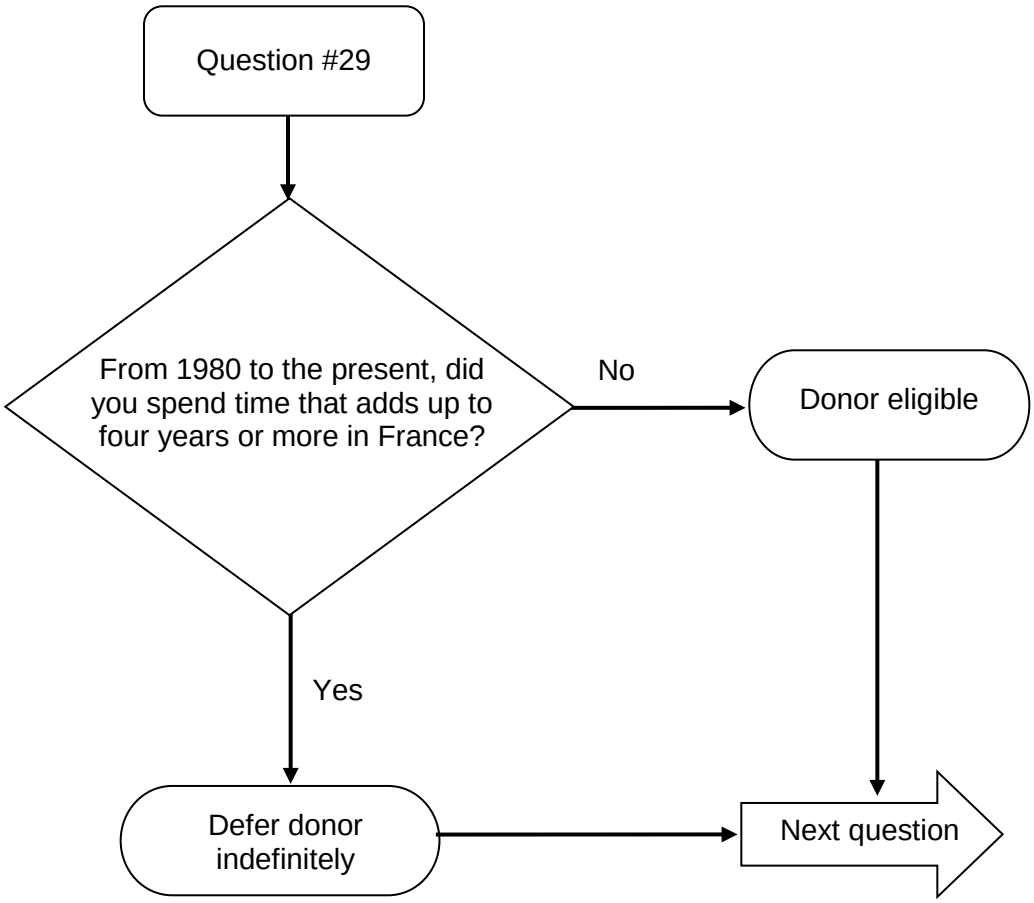
Note: The countries are listed on the Travel Poster and are noted on the map as an additional aid in answering the follow-up question.



Question #29: From 1980 to the present, did you spend time that adds up to four years or more in France?

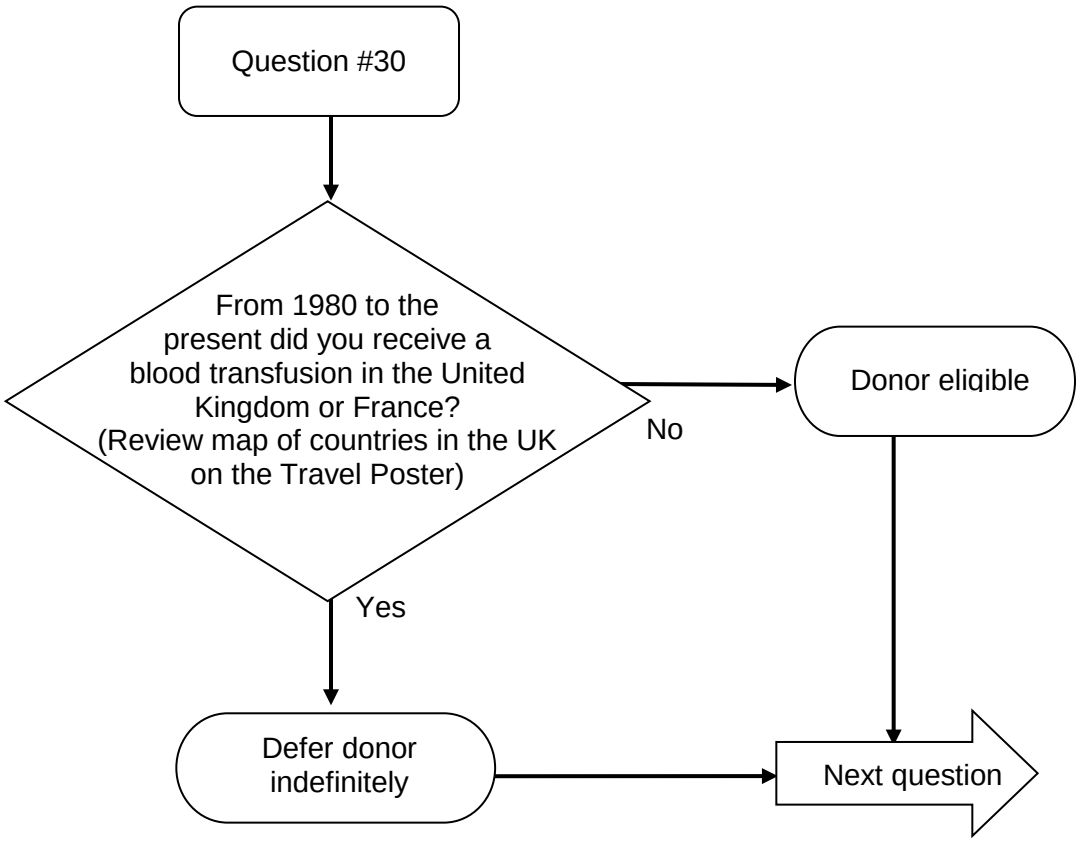
Donor Eligibility: Donors who have spent time that adds up to five years or more in France from 1980 to the present are indefinitely deferred. Donors may be at risk of developing vCJD from eating beef in France.

Note: It was determined that asking the donor if they have spent time up to four years or more in France, which is more restrictive than the FDA regulatory recommendation, allows the question to coincide with the administration of the full length questionnaire to a qualified donor at the required yearly interval. This eliminates the need to ask this question every 4 months within the abbreviated questionnaire.



Question #30: From 1980 to the present did you receive a blood transfusion in the United Kingdom or France? (Review map of countries in the UK on the Travel Poster)

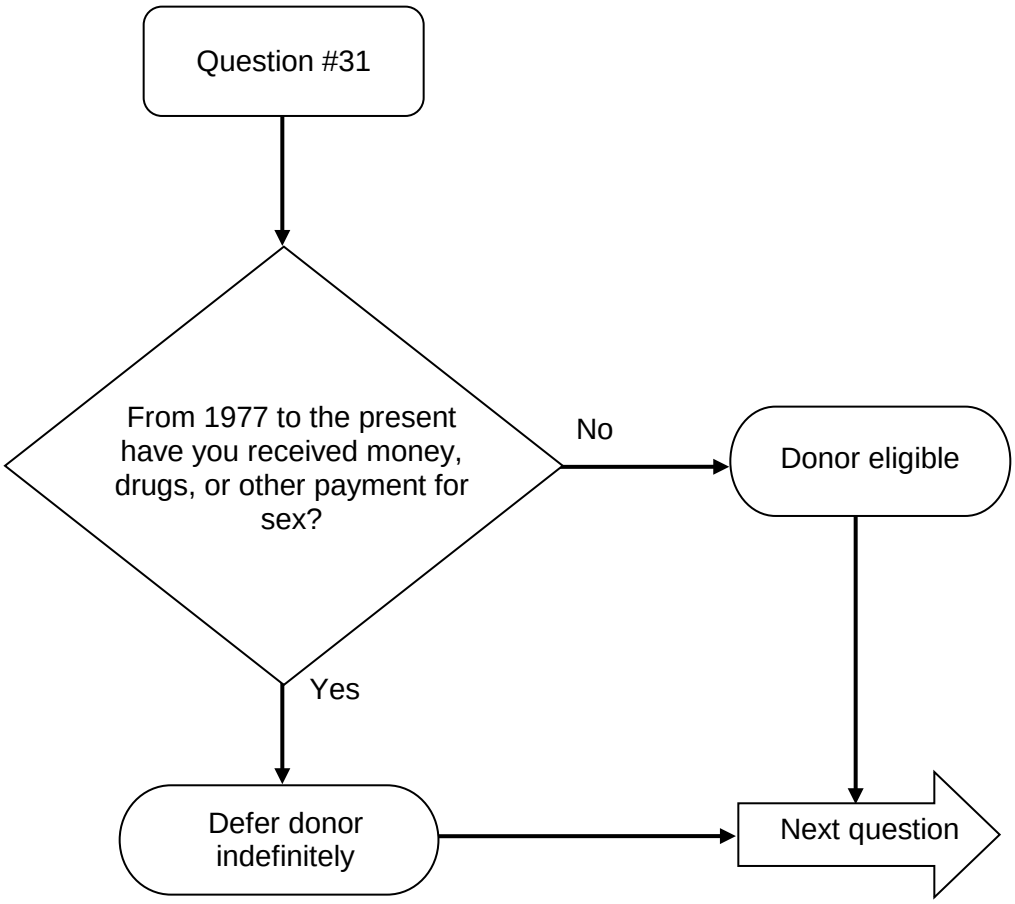
Donor Eligibility: Donors who received a transfusion of blood, platelets, plasma, cryoprecipitate, or granulocytes in the UK (England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands) or France from 1980 to the present are indefinitely deferred. Donors may be at risk of developing vCJD through transfusion.



Question #31: From 1977 to the present have you received money, drugs, or other payment for sex?

Donor Eligibility: Donors who received money, drugs, or other payment for sex are indefinitely deferred. HIV and other diseases may be transmitted by sexual contact.

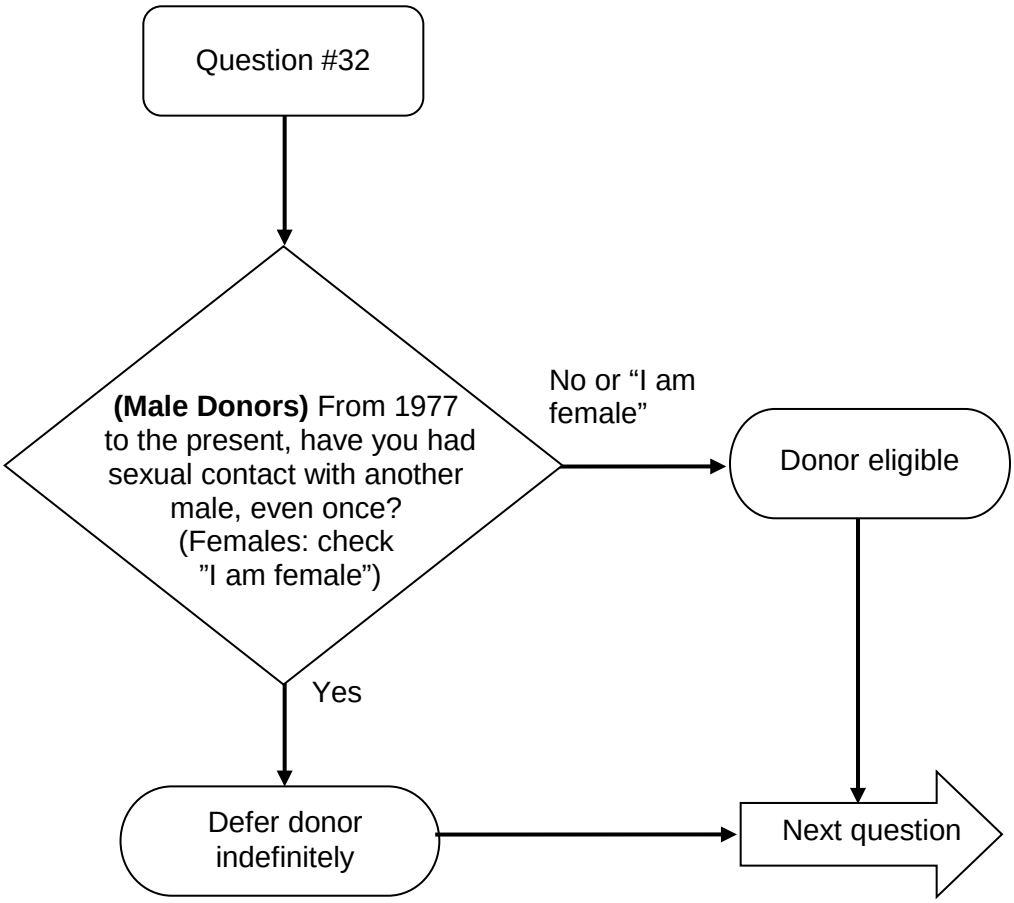
Note: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.



Question #32: (Male Donors) From 1977 to the present, have you had sexual contact with another male, even once? (Females: check ”I am female”)

Donor Eligibility: Male donors who have had sexual contact with another male, even once, since 1977 are indefinitely deferred. Males who have had sex, even once, with males may be at increased risk of transmitting infectious diseases.

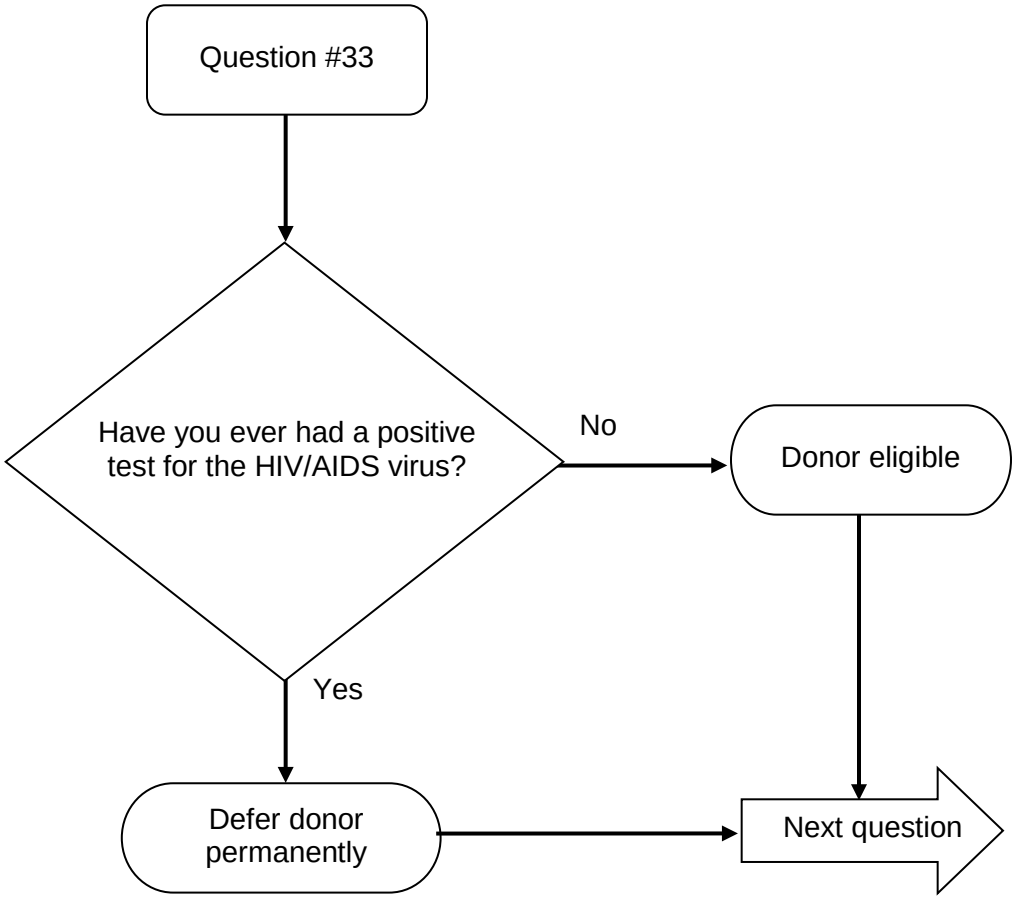
Note: Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster provided.



Question #33: Have you ever had a positive test for the HIV/AIDS virus?

Donor Eligibility: Donors with clinical or laboratory evidence of HIV/AIDS are permanently deferred.

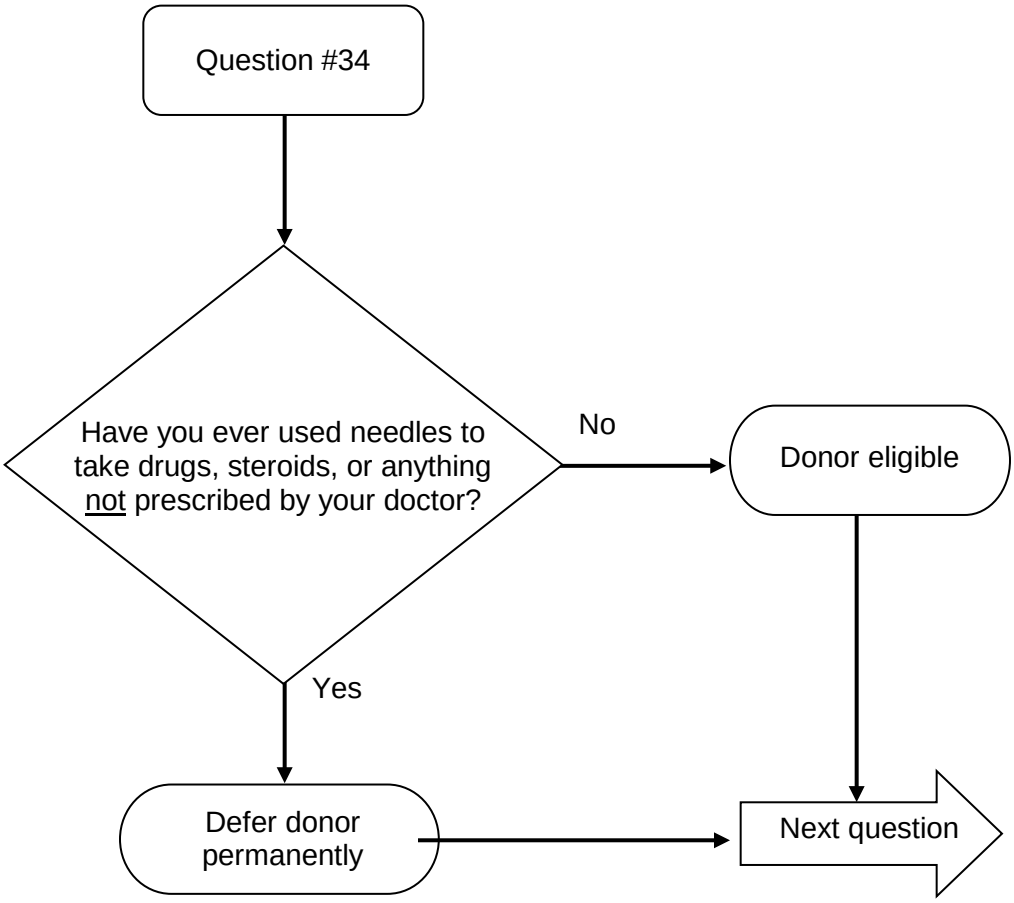
Note: Donors who have been re-entered through FDA-approved protocols may be eligible for donation.



Question #34: Have you ever used needles to take drugs, steroids, or anything not prescribed by your doctor?

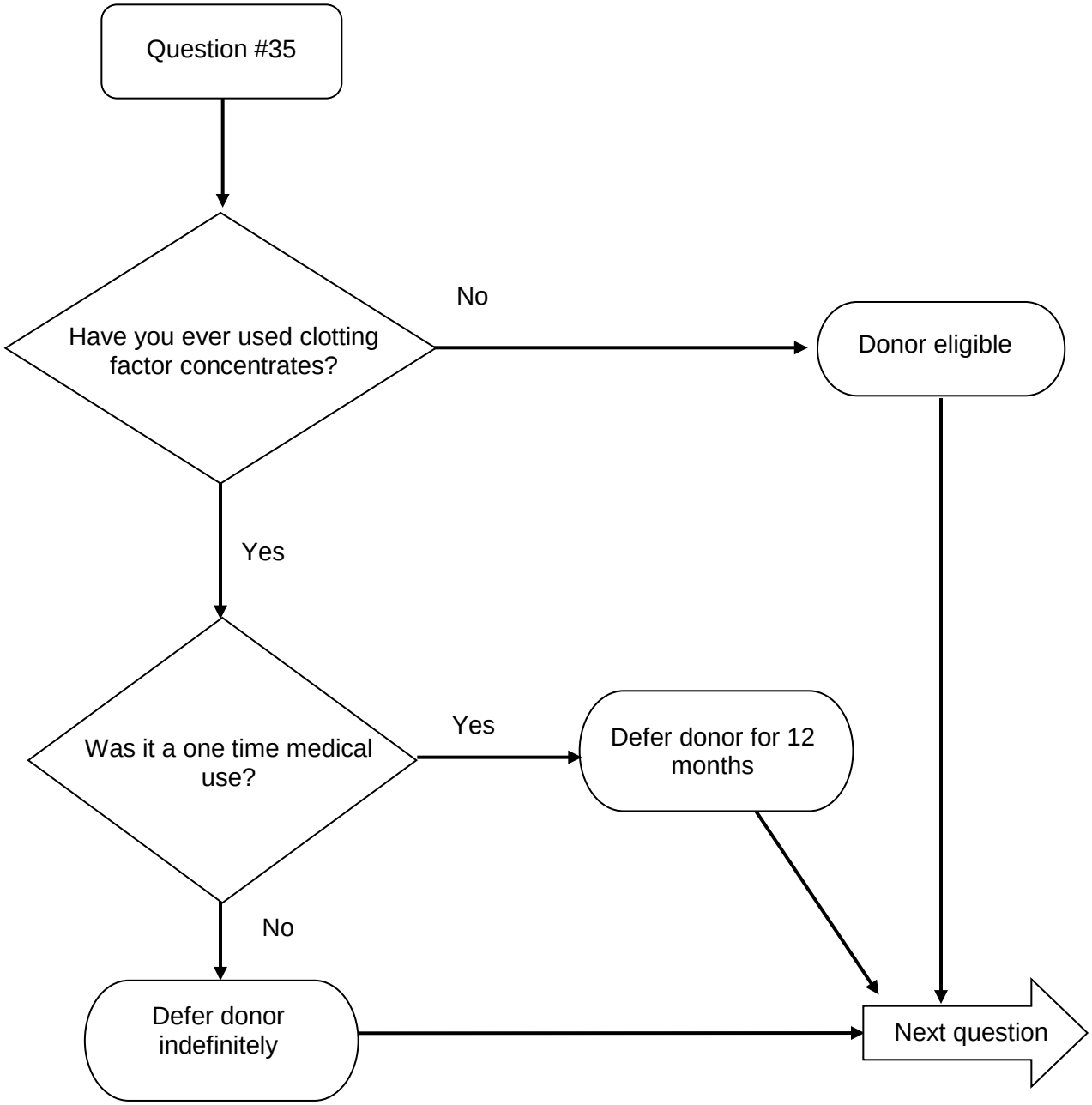
Donor Eligibility: Donors who have taken any drug with a needle are permanently deferred due to potential transmission of infectious disease.

Note: The phrase "use of a needle" includes intravenous use, "skin popping" (injection under the skin), "mainlining" (arterial injection) and any other use of a needle to administer drugs, steroids or anything else not prescribed by their doctor.



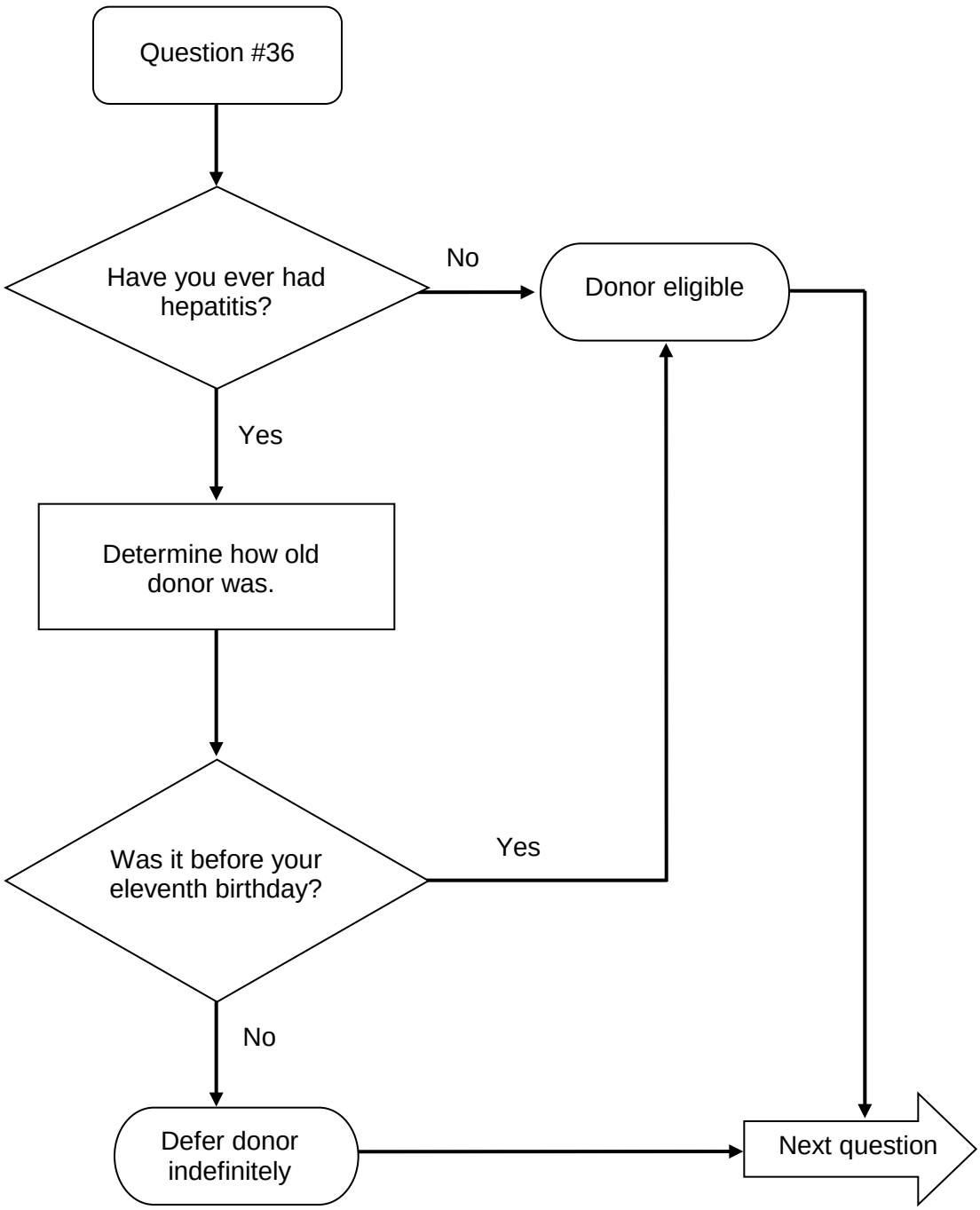
Question #35: Have you ever used clotting factor concentrates?

Donor Eligibility: A donor who has been exposed to clotting factor concentrates should not donate blood due to possible transmissibility of infectious disease.



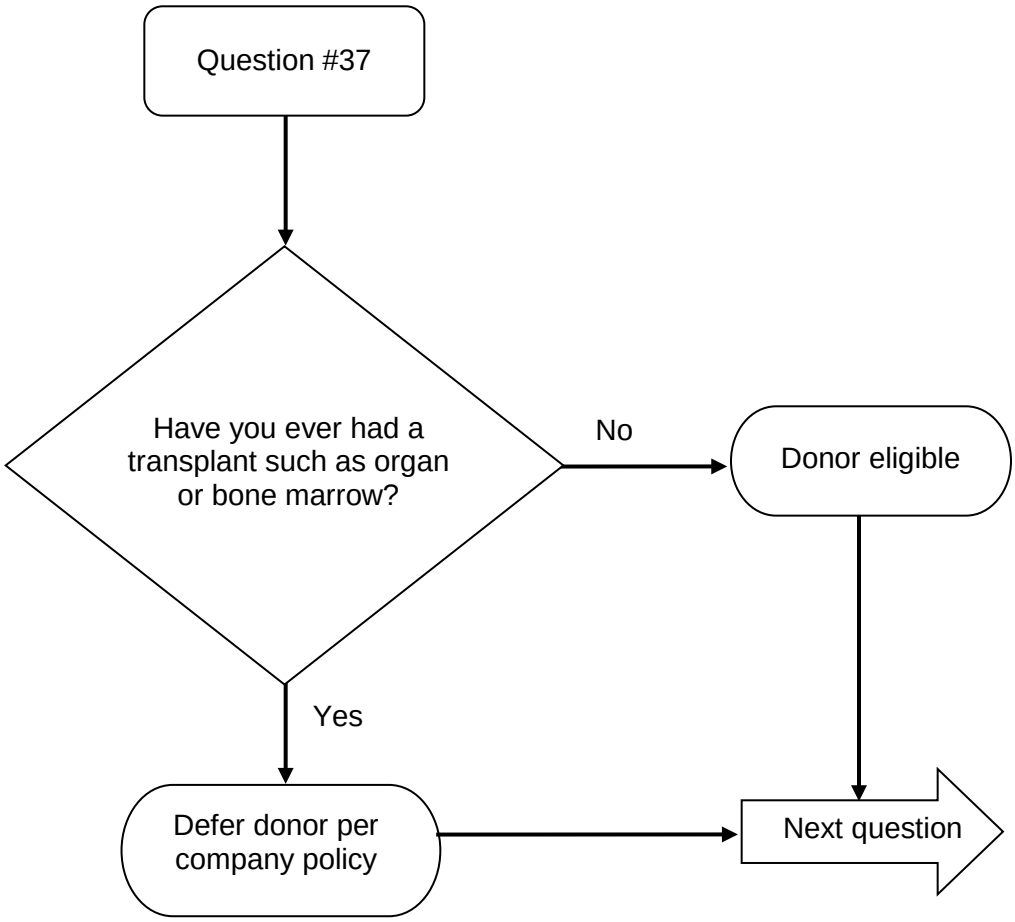
Question #36: Have you ever had hepatitis?

Donor Eligibility: Donors who have a history of viral hepatitis after their eleventh birthday are indefinitely deferred.



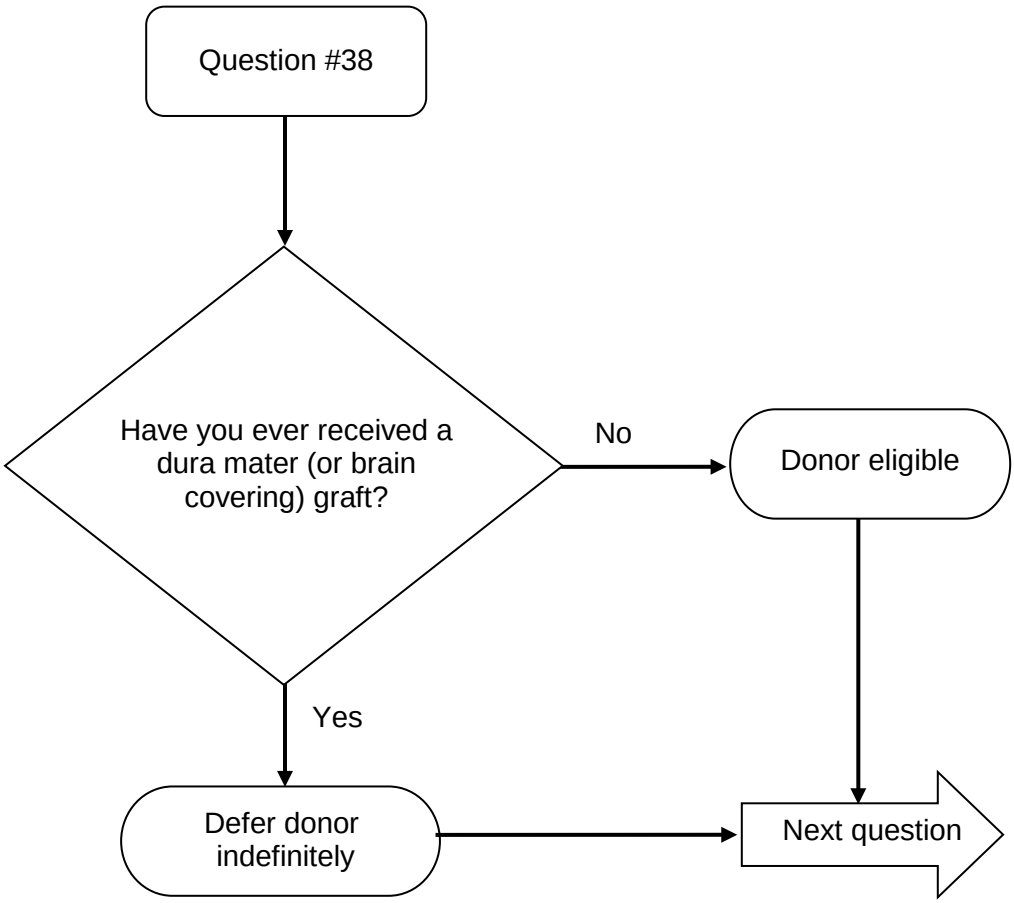
Question #37: Have you ever had a transplant such as organ or bone marrow?

Donor Eligibility: A donor who has had an organ or bone marrow transplant should not donate plasma.



Question #38: Have you ever received a dura mater (or brain covering) graft?

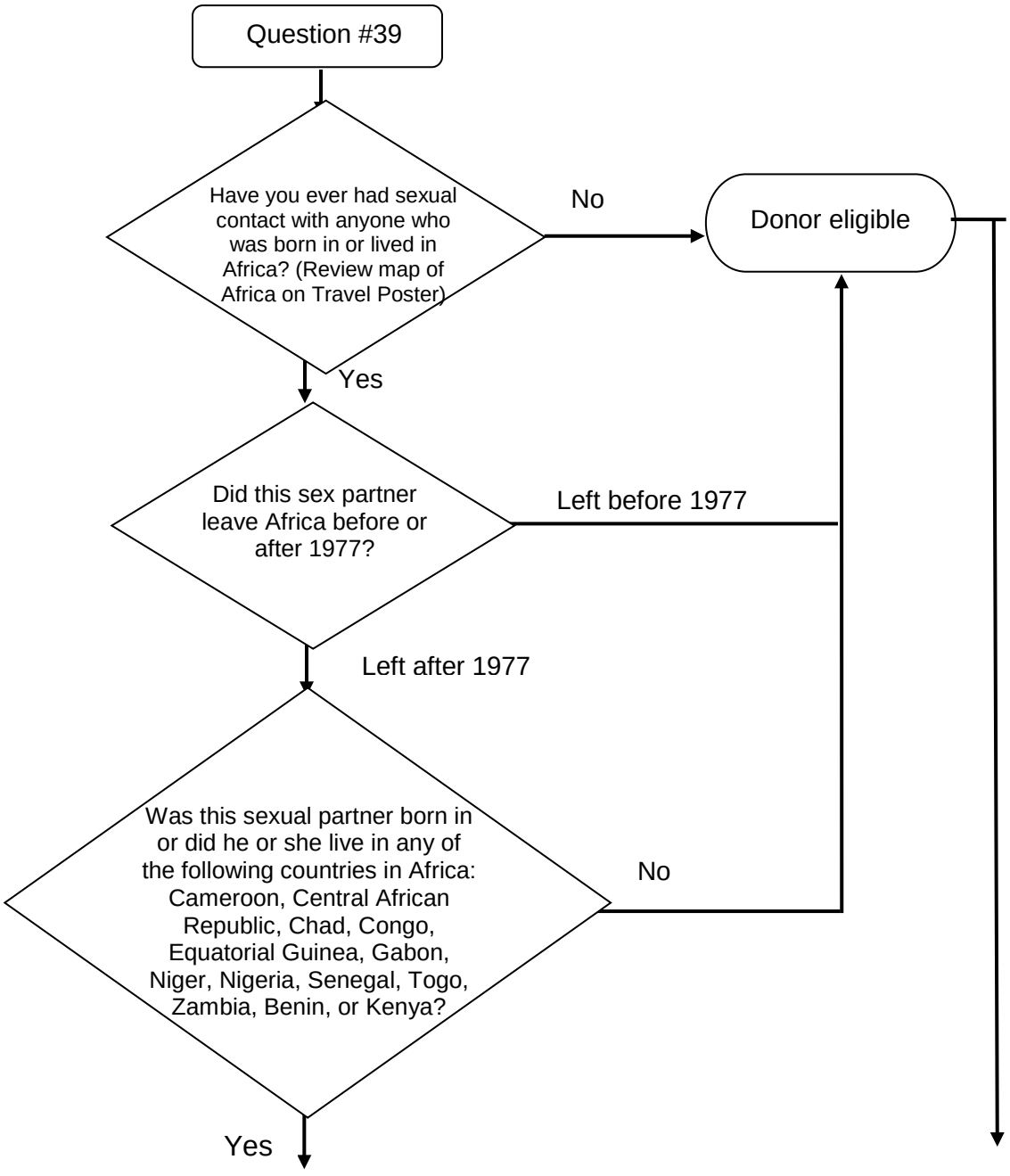
Donor Eligibility: Donors who have received a dura mater transplant or graft may be at risk for Creutzfeldt-Jakob disease and are indefinitely deferred.



Question # 39: Have you ever had sexual contact with anyone who was born in or lived in Africa (Review map of Africa on the Travel Poster)?

Donor Eligibility: If the donor had a sex partner who was born in or lived in certain countries in Africa (see list below) after 1977, the donor is indefinitely deferred. Donors who have had sexual contact may have been exposed to rare strains of HIV that are not detected by current test methods.[2]

Note: 1) Not all donors define "sex" or "sexual contact" in the same way. The donor must have read the Risk Poster. 2) The countries are listed on the Travel Poster and noted on the map as an additional aid in answering the follow-up question.



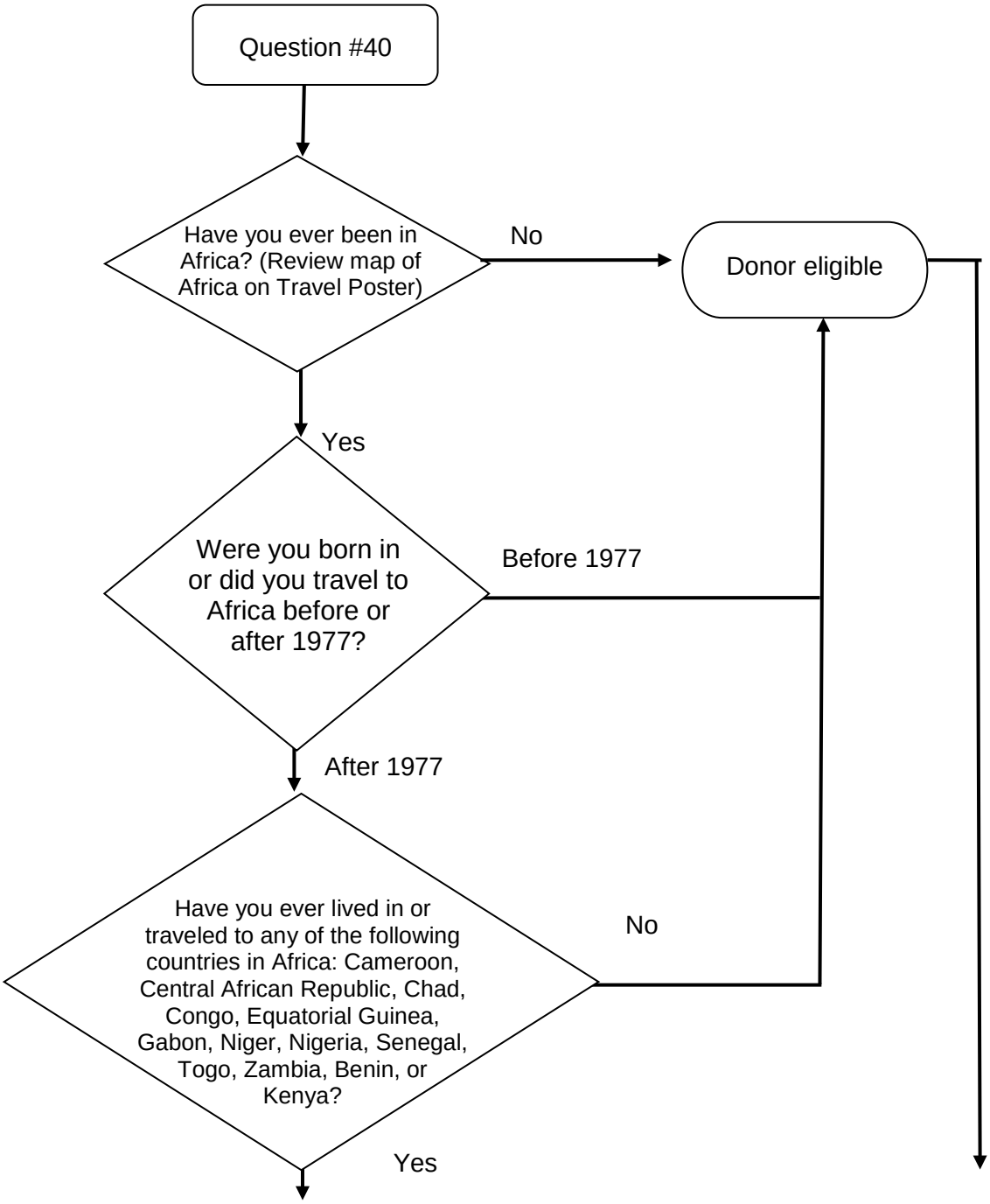
[2] Plasma sourcing organizations using an HIV test that has been approved by FDA to include a donor screening claim for detection of Group O virus may eliminate this question during screening and use the full-length questionnaire that deleted these questions and corresponding risk and travel poster.


Defer Donor
Indefinitely
Next question

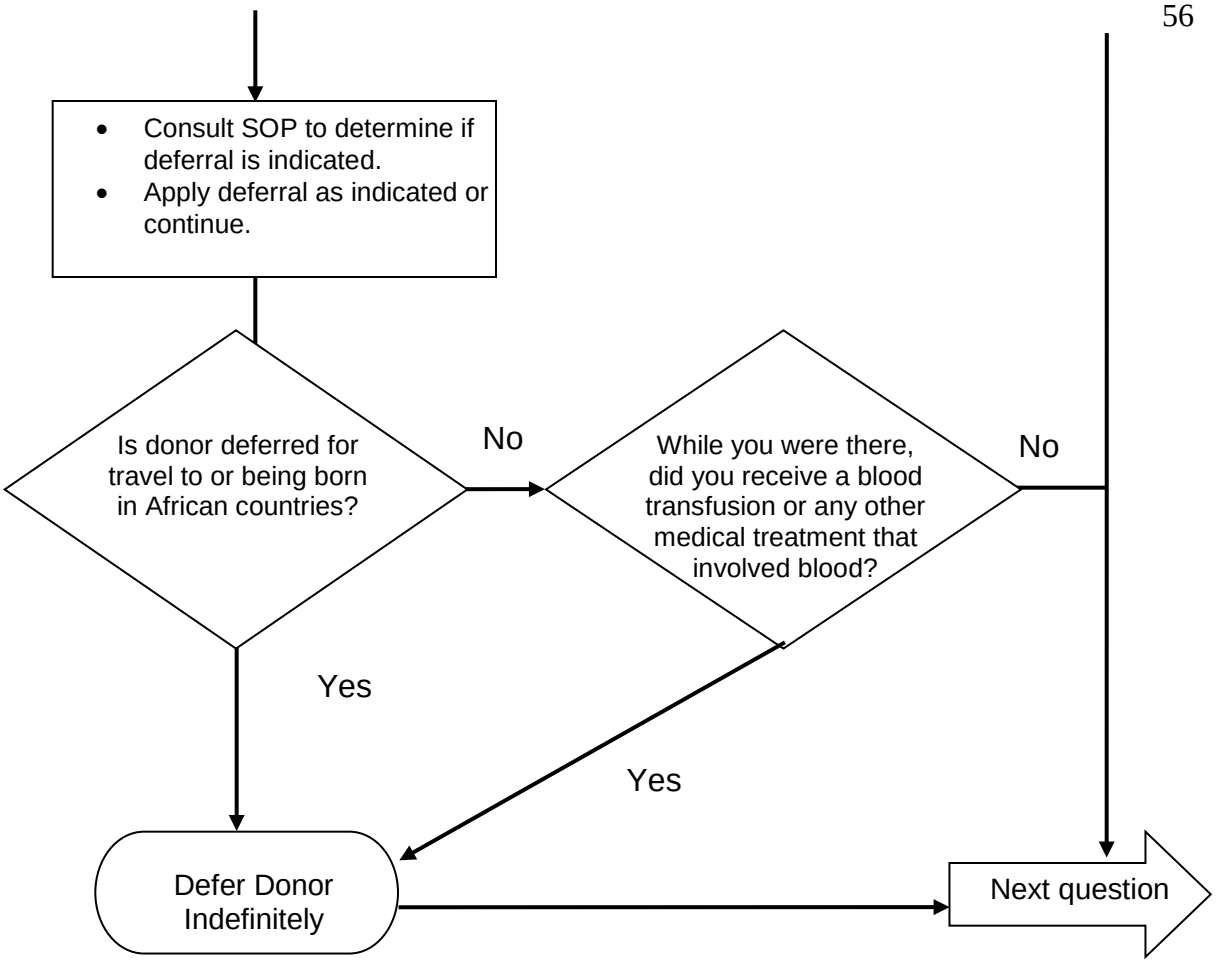
Question # 40: Have you ever been in Africa (Review map of Africa on the Travel Poster)?

Donor Eligibility: Donors who were born in or have lived in certain countries in Africa since 1977 (see list below) are indefinitely deferred. Donors who have received a blood transfusion or any other medical treatment in Africa are indefinitely deferred.[3]

Note: The countries are listed on the Travel Poster and noted on the map as an additional aid in answering the follow-up question.

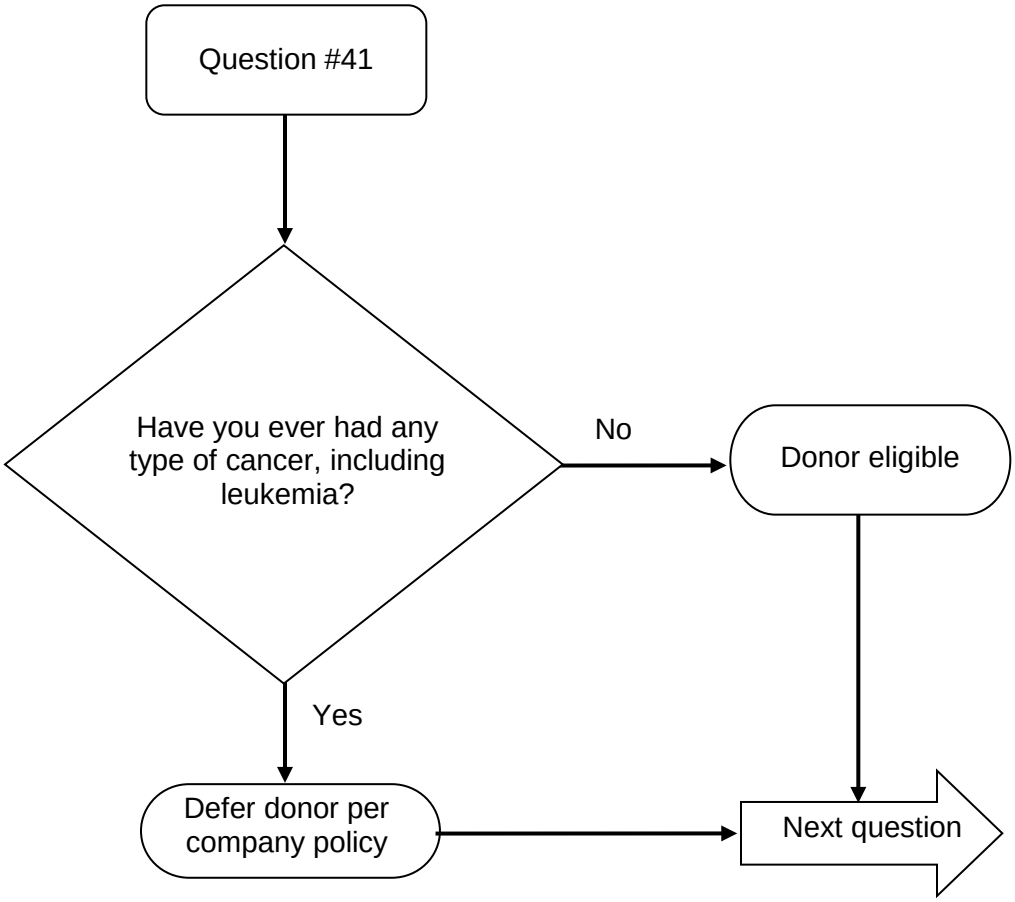


[3] Plasma sourcing organizations using an HIV test that has been approved by FDA to include a donor screening claim for detection of Group O virus may eliminate this question during screening and use the full-length questionnaire that deletes these questions and corresponding risk and travel poster.


Consult SOP to determine if deferral is indicated.
Apply deferral as indicated or continue.
Is donor deferred for travel to or being born in African countries?
No
While you were there, did you receive a blood transfusion or any other medical treatment that involved blood?
No
Yes
Yes
Defer Donor Indefinitely
Next question

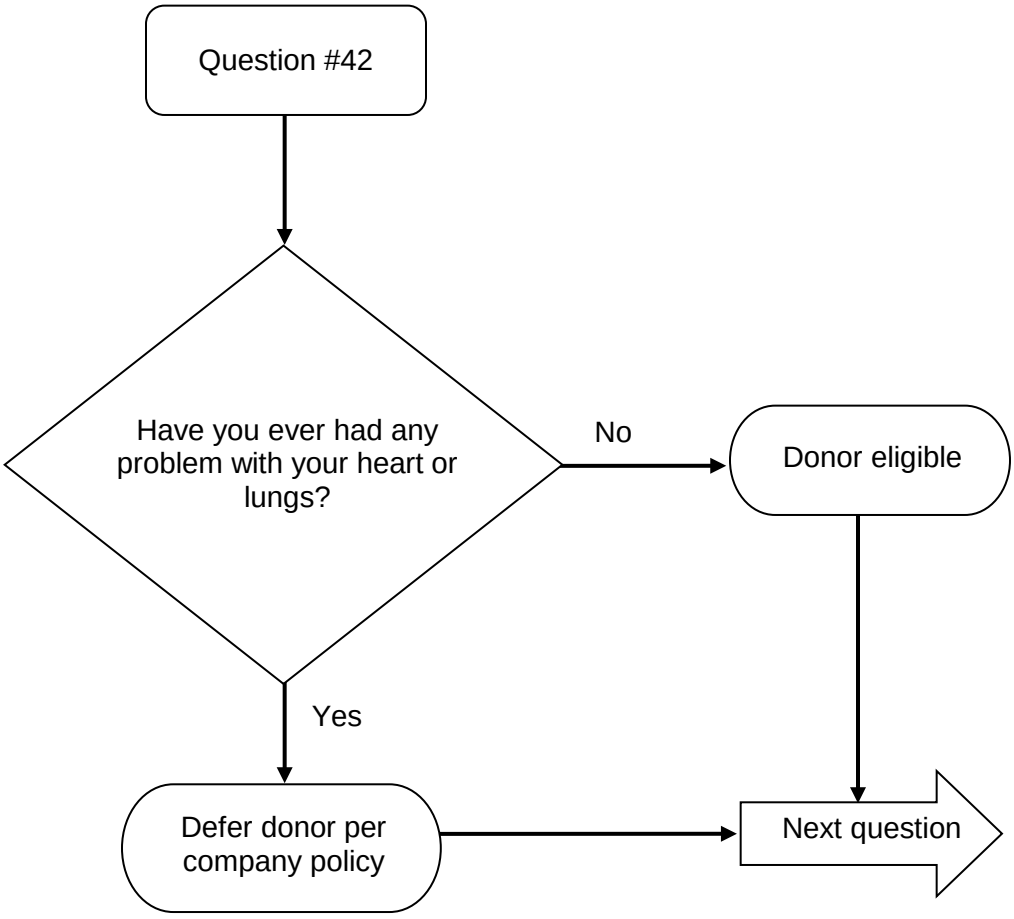
Question #41 (#39 of Full-length Questionnaire I): Have you ever had any type of cancer, including leukemia?

Donor Eligibility: Donors with a history of cancer must be evaluated and deemed eligible to donate per company policy.



Question #42 (#40 of Full-length Questionnaire I): Have you ever had any problem with your heart or lungs?

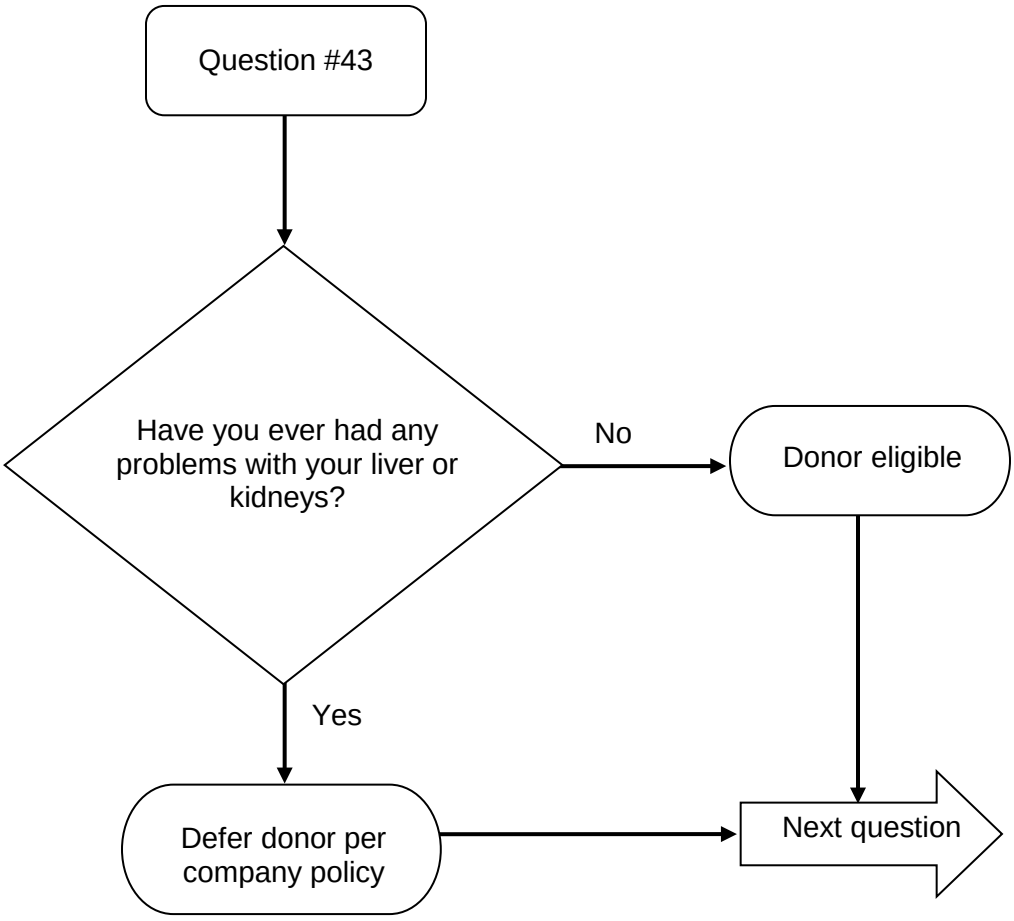
Donor Eligibility: Donors must be free of acute respiratory disease. Donors with a history of diseases of the heart and lungs, including acute diseases, must be evaluated (follow company policy).



Question #43 (#41 of Full-length Questionnaire I): Have you ever had any problems with your liver or kidneys?

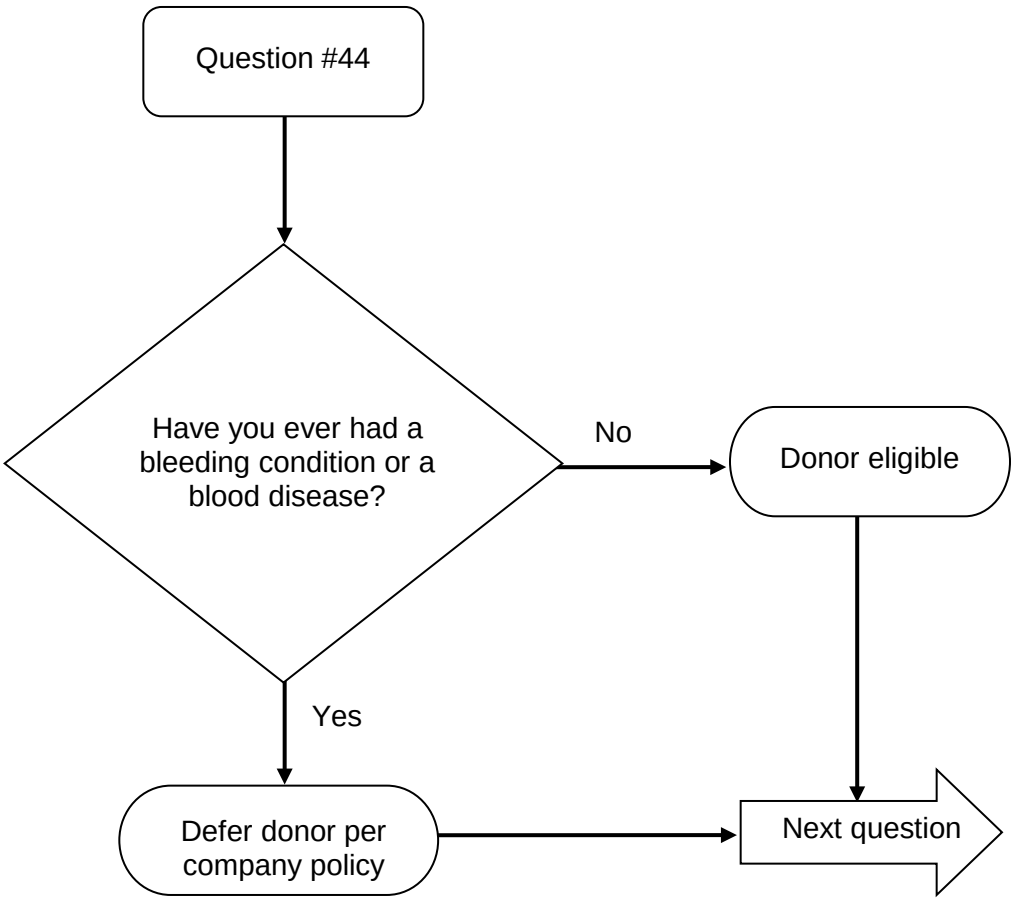
Donor Eligibility: Donors must be free of liver and kidney diseases. Donors with a history of diseases of the liver or kidneys must be evaluated (follow company policy).

Note: If donors need examples of liver and kidney diseases, some examples include: Kidney - kidney stones, renal insufficiency, renal disease, nephritis; and liver – cirrhosis, fatty liver (cholestasis).



Question #44 (#42 of Full-length Questionnaire I): Have you ever had a bleeding condition or a blood disease?

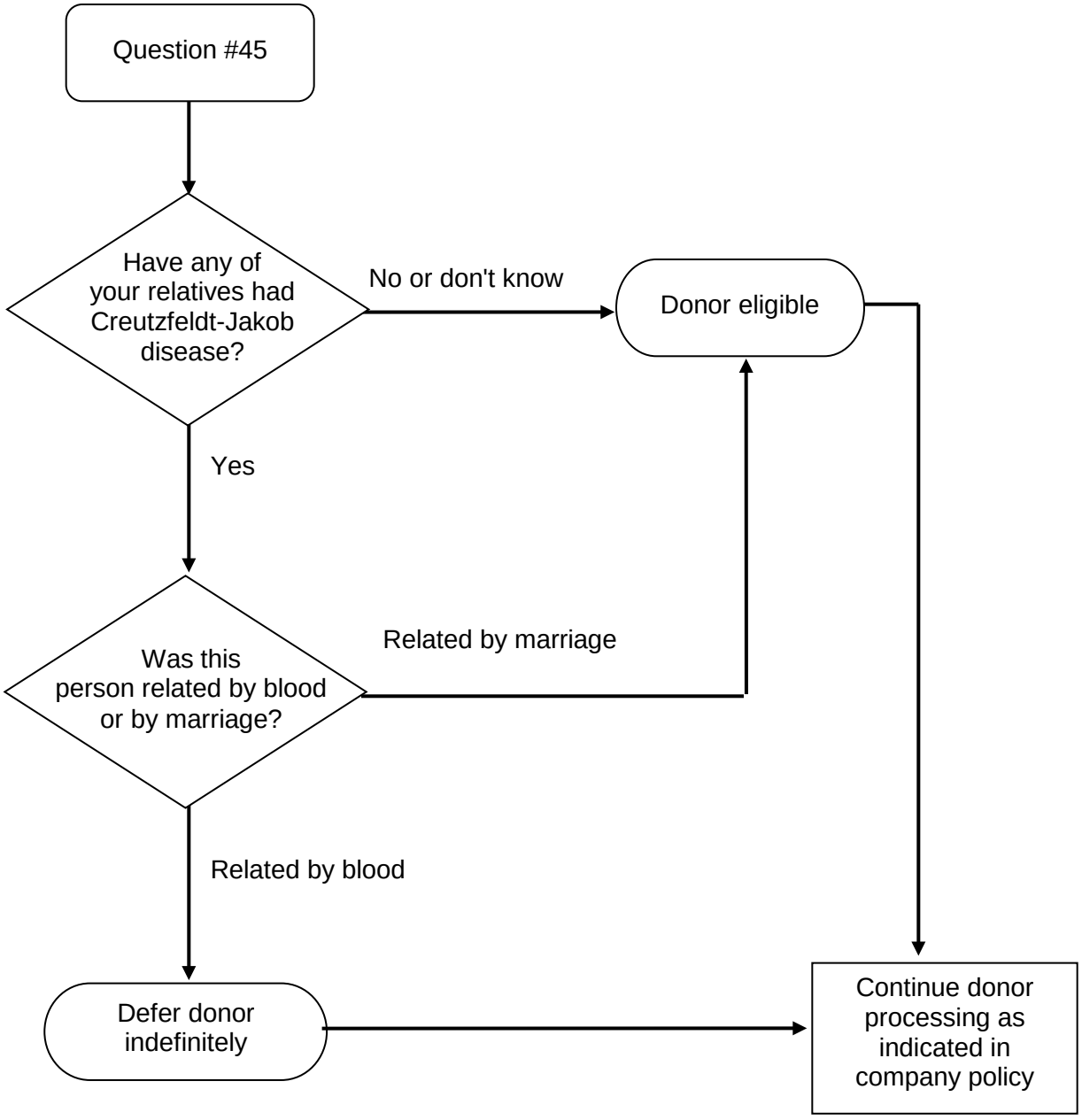
Donor Eligibility: Donors with a history of bleeding problems should be evaluated (follow company policy).



Question #45 (#43 of Full-length Questionnaire I): Have any of your relatives had Creutzfeldt-Jakob disease?

Donor Eligibility: Donors with a blood relative with Creutzfeldt-Jakob disease are indefinitely deferred.

Note: If laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD, the donor may be eligible.



Medication List

Please review this list carefully, and tell us if you are taking or have taken any of these medications.

Medication	Which is also known as…	And is usually used for…	In the last…	You should not donate because the medication may...
Accutane Amnesteem Claravis Myorisan Sotret	Isotretinoin	Severe acne	**Month**	Harm patients who receive medications prepared from your plasma by **causing birth defects in unborn babies**
Propecia	Finasteride	Baldness		
Proscar		Enlarged prostate gland		
Avodart Jalyn	Dutasteride	Enlarged prostate gland	**6 months**	
Soriatane	Acitretin	Severe psoriasis	**3 years**	
Tegison	Etretinate	Severe psoriasis	**Ever**	
HepaGam B HyperHEP B S/D Nabi- HB	Hepatitis B Immune Globulin	Exposure to hepatitis B	**12 months**	Harm patients who receive medications prepared from your plasma by **increasing the risk of transmitting hepatitis**
Growth hormone from human pituitary glands		Delayed growth in children	**Ever**	Harm patients who receive medications prepared from your plasma by **increasing the risk of transmitting CJD or vCJD**
Bovine or beef insulin		Diabetes		
Any experimental or unlicensed vaccine or medication			**Ever**	Harm patients who receive medications prepared from your plasma. Medical evaluation needed.

If you are taking or have taken these medications you may not be eligible to donate PLASMA, whole blood or platelets!

This document is one component of the full-length and abbreviated PPTA donor history questionnaire documents for collection facilities that use an approved test for antibodies to HIV that detect HIV-1 Group O. The full-length and abbreviated PPTA donor history questionnaire documents must be used collectively.

Source Plasma Industry Risk Poster I

Sexual contact means any of the following (whether or not a condom or barrier device was used):

- Vaginal intercourse **(contact between penis and vagina)**
- Oral sex **(mouth or tongue on someone's vagina, penis, or anus)**
- Anal intercourse **(contact between penis and anus).**

Do NOT donate PLASMA, whole blood or platelets if you…

Ever

- **Had HIV/AIDS** (see list of **symptoms** below)
- Had **a positive test for HIV** (**AIDS** virus)
- Had a **positive test for hepatitis**
- **Had hepatitis** (**after** your **11th birthday**)
- Used **needles** to take **drugs**, **steroids** or anything not prescribed by your doctor
- **Used clotting factor concentrates** for a bleeding disorder
- Had a transplant such as **organ** or **bone marrow**

Since 1977

- **Received money, drugs** or other payment for **sex**
- **(Male donors**) Had **sexual contact** with **another male**, even once

In the last 12 months

- Have **given money, drugs or other payment for sex**
- Have been **treated** for
  - **syphilis**
  - **gonorrhea**
- "Lived with" a person who has **hepatitis** (lived at same residence and shared kitchen and bathroom)
- **Had** a **blood** transfusion or received other blood products
- Received during surgery **bone, tissue** or **skin**
- Had an **accidental needle-stick** involving exposure to blood
- Had **contact** with **someone else's blood**
- Had a **tattoo applied**
- Had **ear or body piercing**
- Have **been in**
  - **juvenile detention**
  - **lock up**
  - **jail**
  - **prison**

  For more than **72 hours**

Had sexual contact with anyone who:

- **Has HIV/AIDS** (see list of symptoms below)
- Has **a positive test for HIV** (**AIDS** virus)
- **Has hepatitis**
- Used **needles** to take **drugs**, **steroids** or anything not prescribed by their doctor
- Has **hemophilia** or has **used clotting factor concentrates**
- (Female donors) Had sexual contact with a male who has had sexual contact with another male, even once

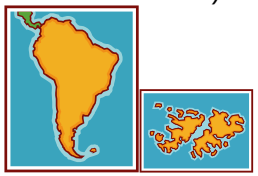
Signs or **symptoms** of **HIV/AIDS:**

- Unexplained **weight loss**
- **Night sweats**
- **Blue or purple spots** in your mouth or skin
- **White spots** or unusual sores in your mouth
- **Swollen lymph nodes** for more than one month
- **Fever** of more than100.5 ^{o}F for more than 10 days
- **Cough** that won't go away
- **Shortness of breath**
- **Diarrhea** that won't go away

This document is one component of the full-length PPTA donor history questionnaire documents for source plasma organizations that use a test for antibodies to HIV that detects HIV-1 group O. The full length PPTA donor history questionnaire documents must be used collectively.

Travel Poster I

<table>
<tr><th>Area</th><th>Country</th><th>Type of Travel or Residence</th><th>Time Period</th><th>Deferral Period</th><th>Reason for Deferral</th></tr>
<tr><td rowspan="5">Europe
 

Falkland Islands
(off the Eastern coast of South America)
  </td><td>• England
• Northern Ireland
• Scotland
• Wales
• The Isle of Man
• The Channel Islands
• Gibraltar
• The Falkland Islands</td><td>3 months or more</td><td>Between 1980 and 1996</td><td rowspan="5">Indefinite</td><td rowspan="5">Possible risk of vCJD

(There is no test for vCJD)</td></tr>
<tr><td></td><td>Received a blood transfusion in</td><td>Since 1980</td></tr>
<tr><td>• France</td><td>4 years or more and/or received a blood transfusion in</td><td>Since 1980</td></tr>
<tr><td>• Belgium
• Netherlands
• Germany</td><td>6 months or more associated with a US military base</td><td>Between 1980 and 1990</td></tr>
<tr><td>• Spain
• Portugal
• Turkey
• Italy
• Greece</td><td>6 months or more associated with a US military base</td><td>Between 1980 and 1996</td></tr>
</table>

感染症定期報告に関する今後の対応について

平成１６年度第５回
運営委員会確認事項
（平成１６年９月１７日）

１ 基本的な方針

運営委員会に報告する資料においては、

(1) 文献報告は、同一報告に由来するものの重複を廃した一覧表を作成すること。

(2) 8月の運営委員会において、国内の輸血及び血漿分画製剤の使用した個別症例の感染症発生報告は、定期的にまとめた「感染症報告事例のまとめ」を運営委員会に提出する取り扱いとされた。これにより、感染症定期報告に添付される過去の感染症発生症例報告よりも、直近の「感染症報告事例のまとめ」を主として利用することとすること。

２ 具体的な方法

(1) 感染症定期報告の内容は、原則、すべて運営委員会委員に送付することとするが、次の資料概要を作成し、委員の資料の確認を効率的かつ効果的に行うことができるようにする。

① 研究報告は、同一文献による重複を廃した別紙のような形式の一覧表を作成し、当該一覧表に代表的なものの報告様式（別紙様式第2）及び該当文献を添付した**「資料概要A」**を事務局が作成し、送付する。

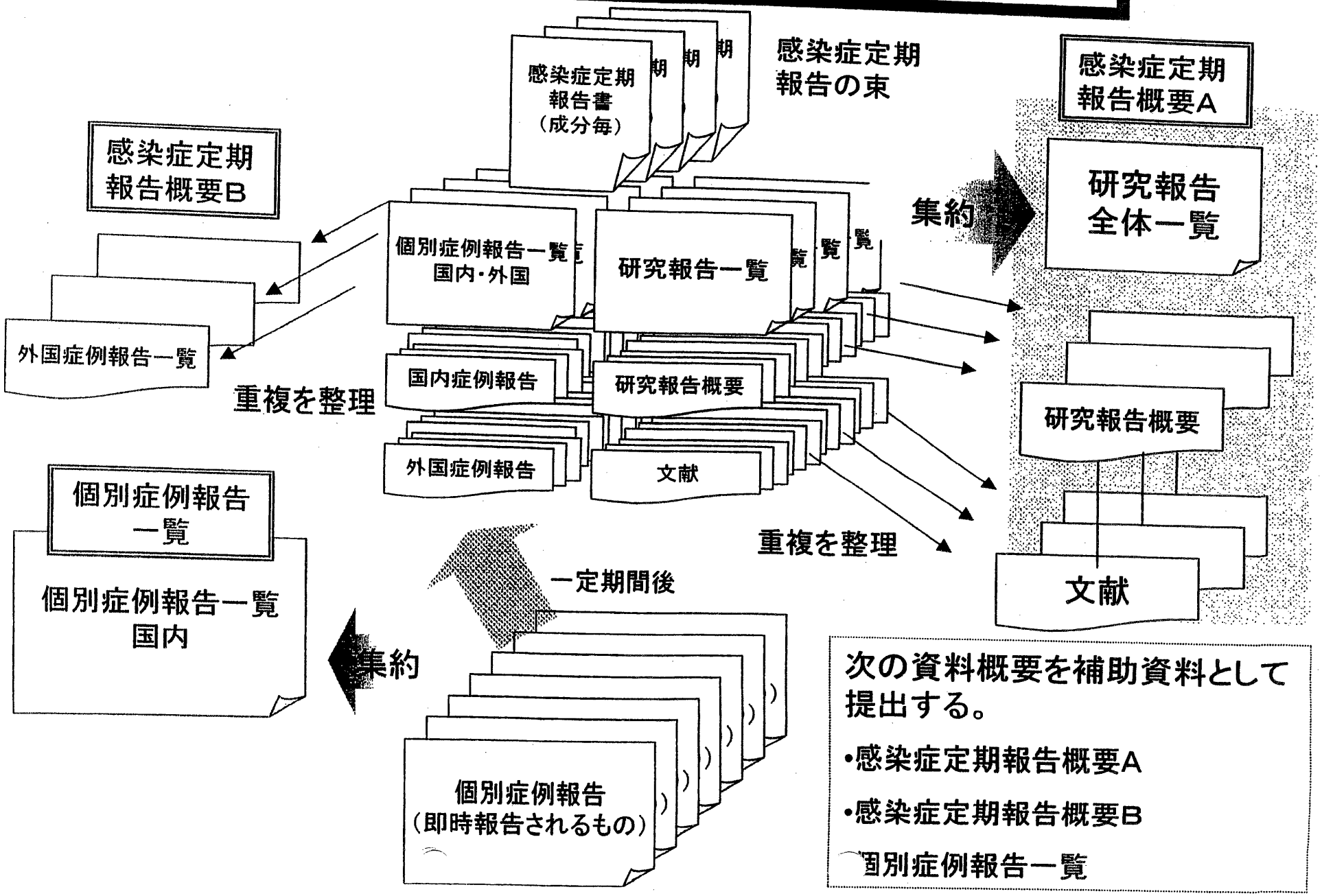
② 感染症発生症例報告のうち、発現国が「外国」の血漿分画製剤の使用による症例は、同一製品毎に報告期間を代表する感染症発生症例一覧（別紙様式第4）をまとめた**「資料概要B」**を事務局が作成し、送付する。

③ 感染症発生症例報告のうち、発現国が「国内」の輸血による症例及び血漿分画製剤の使用による感染症症例については、「感染症報告事例のまとめ」を提出することから、当該症例にかかる「資料概要」は作成しないこととする。ただし、運営委員会委員から特段の議論が必要との指摘がなされたものについては、別途事務局が資料を作成する。

(2) 発現国が「外国」の感染症発生症例報告については、国内で使用しているロットと関係がないもの、使用時期が相当程度古いもの、因果関係についての詳細情報の入手が困難であるものが多く、必ずしも緊急性が高くないと考えられるものも少なくない。また、国内症例に比べて個別症例を分析・評価することが難しいものが多いため、緊急性があると考えられるものを除き、その安全対策への利用については、引き続き、検討を行う。

(3) 資料概要A及びBについては、平成16年9月の運営委員会から試験的に作成し、以後「感染症的報告について（目次）」資料は廃止することとする。

感染症定期報告・感染症個別症例報告の取り扱い



次の資料概要を補助資料として提出する。

- 感染症定期報告概要A
- 感染症定期報告概要B
- 個別症例報告一覧