older PLT units where low initial concentrations of bacteria with a prolonged lag phase that are missed due to sampling limitations may reach significant concentrations by the time of transfusion.

Division of the PLT sample between an anaerobic and aerobic bottle in the BacT/ALERT system has been recommended by the manufacturer to increase bacterial culture sensitivity and is currently under investigation in the PASSPORT protocol for extended storage PLTs.[13] The anaerobic culture bottle may detect obligate anaerobes that occasionally contaminate PLT products[9,35] as well as increase the sensitivity and decrease the time required for detection of some facultative aerobic organisms, including *Staphylococcus* sp. and *Streptococcus* sp.[36] Anaerobic testing, however, increases product losses and hospital recalls due to increased false-positive culture results and substantially increases the cost per test performed, due to the additional costs of the anaerobic bottle and the corresponding increase in the number of incubators required. Early studies in the United States have failed to demonstrate increased sensitivity for common PLT contaminants in routine practice.[37] Interpretation of European studies is confounded by poor differentiation between true- and false-positive initial culture results; however, the data support the view that the volume of product cultured, not necessarily the culture conditions, is an important determinant of culture sensitivity for common aerobic PLT contaminants.[27] More rapid detection of bacterial contamination will likely have little impact on safety, because our data demonstrate that septic reactions are associated with false-negative culture results that do not become positive even after prolonged incubation. We also describe 97 instances where delayed initial-positive culture results allowed PLT products to be transfused before detection. Earlier detection of bacterial growth may have prevented these transfusions; however, none of these cases were associated with a septic transfusion reaction.

Obligate anaerobes such as *Clostridium* sp. and *Propionibacterium acnes* are likely skin contaminants, which may be more effectively mitigated by diverting the initial sample from the draw line (e.g., sample first/diversion pouch strategies) than detection strategies that have inherent sampling and sensitivity limitations.[9,35,38] *Clostridium* spp. and *Eubacterium* spp., in particular, are anaerobes that have been associated with fatalities.[35,39,40] The detection of *Clostridium* sp. has been validated in pooled whole blood–derived PLTs; however, at spiking concentrations of 0.2 CFUs per mL, the BacT/ALERT system failed to detect contamination in 7 of 10 samples tested.[41] At higher concentration (1.9 CFU/mL), *Clostridium perfringens* was reliably detected in 10 of 10 anaerobic bottles.[41] The authors are not aware of instances where *Clostridium* sp. or *Eubacterium* sp. have been detected by anaerobic bottles in routine apheresis PLT cultures.[9,27,37,42] Interestingly, there are reports of both *P. acnes* and *Clostridium* sp. detection in aerobic BacT/ALERT bottles.[43,44] These observations raise the possibility that the clinically significant anaerobes are those that grow as facultative aerobes in the aerobic conditions of PLT storage.

Reports of septic reactions and fatalities persist despite the implementation of both aerobic and anaerobic cultures: de Korte and coworkers[27] report two cases of sepsis caused by units contaminated with *Bacillus cereus* bacteria and recently Schmidt and coworkers[45] reported both a fatality and a severe septic reaction case caused by the two split units of an apheresis product later found to be contaminated with *Klebsiella pneumoniae* bacteria. These data, and our finding that septic reactions and fatalities are more likely with PLTs transfused on Day 5 after collection despite the report that the majority of PLTs are transfused on Day 3 or earlier,[22] now raise concerns about an increasing residual risk of sepsis with PLT storage age and the safety of extending PLT storage beyond 5 days.

Finally, bacterial screening of apheresis PLT donors has provided a unique opportunity for a secondary public health benefit. Donor centers investigating bacterial cultures and recipient reactions have recommended medical referral for donors with possible asymptomatic bacteremia, which in rare cases has led to early identification of serious medical conditions, including adenocarcinoma of the colon,[21,46] bacterial endocarditis,[2] and subclinical osteomyelitis.[47] Most importantly, as demonstrated in this report, the ongoing surveillance for bacterial detection among blood donors allowed for the identification of a possible design flaw in two-arm collection procedures. Bacterial contamination remains a serious risk of PLT transfusion despite bacterial culture testing, emphasizing the need for the appropriate clinical use of PLT transfusions and ongoing vigilance to recognize, investigate, promptly treat, and report all suspected septic transfusion reactions.

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研究報告の概要

高病原性鳥インフルエンザウイルス(H5N1)を含むインフルエンザウイルスが、(輸血用)血液の脅威となる可能性がある。当研究チームはミニプール核酸増幅法を用いて 10,272 名の血液ドナーの検体を解析した。この検査法の測定感度は、一般的インフルエンザウイルス用プライマーについては 804 geq/ml で、インフルエンザ(H5N1)サブタイプ特異的プライマーでは 444 geq/ml であった。本研究は、インフルエンザウイルスに対して、このようなスクリーニング検査が可能であることを示した。
血液製剤の安全性を確保するため、このスクリーニング法を、世界的流行の際に遅滞なく血液スクリーニング手順に導入できるであろう。今回のインフルエンザスクリーニング方法の感度は、現在報告されている感染者血漿でのウイルス濃度を検知するのに十分であると考えられる。しかし、すべてのミニプール法と同様、ドナーのウイルス血症レベルがスクリーニングアッセイ法の測定感度以下であるために(スクリーニング検査で除外されず)稀に感染が輸血レシピエントに伝播されることがありうる。
こうしたリスクを減少させるため、米国でウエストナイルウイルススクリーニングに導入されているように、selective infectious dose NAT strategy (例えば、標準のミニプールスクリーニングアルゴリズムによって、週当たり少なくとも 1 件のウイルス血症血液が採取された場合に、infectious dose NAT 検査を開始する)が必要となるかもしれない。

使用上の注意記載状況・その他参考事項等

代表として献血ヴェノグロブリン-IH ヨシトミの記載を示す。
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-I 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濾過膜処理（ナノフィルトレーション）及び pH3.9～4.4 の条件下での液状インキュベーション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。

報告企業の意見	今後の対応
高病原性トリインフルエンザ A (H5N1) ウイルスを含むインフルエンザウイルスに対するスクリーニング検査が、ミニプール NAT により実施可能であることが示されたとの報告である。 血漿分画製剤からの高病原性トリインフルエンザA（H5N1）ウイルス伝播の事例は報告されていない。また、万一原料血漿に高病原性トリインフルエンザA（H5N1）ウイルスが混入したとしても、BVDをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・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。

Blood Screening for Influenza

Michael Kai Hourfar,* Anna Themann,* Markus Eickmann,† Pilaipan Puthavathana,‡ Thomas Laue,§ Erhard Seifried,* and Michael Schmidt*

Influenza viruses, including highly pathogenic avian influenza virus (H5N1), could threaten blood safety. We analyzed 10,272 blood donor samples with a minipool nucleic acid amplication technique. Analytical sensitivity of the method was 804 geq/mL and 444 geq/mL for generic influenza primers and influenza (H5N1) subtype–specific primers. This study demonstrates that such screening for influenza viruses is feasible.

In the 20th century, 3 influenza-related pandemics occurred (1918 Spanish influenza, 1957 Asian influenza, and 1968 Hong Kong influenza) (*1*), which are now known to represent 3 different antigenic subtypes of the influenza A virus: H1N1, H2N2, and H3N2. Major influenza epidemics show neither periodicity nor a predictable pattern, and all differ from one another. Evidence suggests that true pandemics involving changes in hemagglutinin subtypes are caused by genetic reassortment in animal influenza A viruses. Since 2003, the World Health Organization has reported the infection of ≈218 persons and 124 deaths (56.9%; as of May 23, 2006) caused by the (H5N1) subtype in 10 different countries; a probable person-to-person transmission of the avian influenza virus was suggested (*2*). Most countries predicted death rates of 14–1,685 persons per 100,000 population in the event of a pandemic and estimated that up to 2,707 persons per 100,000 population would become infected (*3*).

Our study demonstrates that screening donor blood for influenza A (H5N1) subtype or for influenza viruses in general by minipool nucleic acid amplification technique (NAT) is feasible. To ensure the safety of blood products, this screening technique could be introduced into the blood-screening procedure without delay in the case of a pandemic.

The Study

To increase blood safety, we introduced minipool NAT screening in our blood donor service in 1997 for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV-1 and in 2000 for hepatitis A virus (HAV) and parvovirus B19 (*4*). For these purposes, 100-µL aliquots of up to 96 blood samples were pooled. The complete pool of up to 9.6 mL was centrifuged at 58,000× *g* for 60 min at 4°C. Viruses were extracted by using spin columns, and nucleic acid was eluted in a total volume of 75 µL. Only 60 µL of extract is needed for routine NAT screening. A residual volume of 15 µL can then be used for additional NAT testing (*5*) for influenza viruses.

The real-time quantitative amplification of influenza/H5 was performed according to the manufacturer's instructions (Artus Influenza/H5 LC RT-PCR Kit, QIAGEN, Hamburg, Germany) by using a thermocycler (LightCycler; Roche Applied Science, Mannheim, Germany). The test consists of 2 individual amplification reactions. In the first step, a generic influenza PCR is performed. The specificity of this reaction was demonstrated for all subtypes of influenza A (H1–H15, N1–N9) and all subtypes of influenza B. Samples with a positive test result in the first PCR were analyzed in a second PCR with influenza (H5N1)–specific primers and probes. Therefore, the assay allows differentiation between avian influenza (H5N1) and other influenza virus strains.

To mimic a situation like an H5-positive donation, a purified culture supernatant of Vero cells infected with influenza (H5N1) (strain A/Thailand/1 (KAN-1)/2004) (*6*) was used as an external quantification standard. Virion integrity in this preparation was confirmed by electron microscopy. The viral RNA concentration was determined in an external laboratory by multiple quantitative real-time PCR determinations (*7*). Different dilutions of the external influenza (H5N1) subtype quantification standard (0.0, 0.91, 1.96, 3.91, 7.81, 15.63, 31.25, 62.5, 125, and 250 PFU/mL) were prepared, and 100 µL of each dilution was spiked into 9.5-mL negative plasma pools. Each dilution was repeatedly spiked and tested in 8 minipools. Five microliters of the extract was analyzed with the generic influenza NAT as well as with the specific influenza (H5N1) NAT. Results are shown in Tables 1 and 2. Probit analysis of these data yielded a detection probability of >95% in parallel tests when an average of at least 13.4 PFU/mL (95% confidence interval [CI] 8.3–184 PFU/mL) and 7.4 PFU/mL (95% CI 5.2–14.7 PFU/mL) for influenza generic assay and for the influenza (H5N1)–specific test, respectively, were present in individual plasma samples before pooling.

A total of 117 routine minipools, representing 10,272 blood donor samples, containing an average of 88 ± 8 samples per pool, had previously been tested for HIV-1, HBV, HCV, HAV, and parvovirus B19. All pools were negative for influenza virus when tested with the generic influenza PCR and the influenza (H5N1)–specific PCR. One pool had invalid results (failed amplification of internal control RNA, representing 0.01% of all analyzed runs).

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Table 1. Analytical sensitivity for influenza virus in plasma samples*

PFU (H5N1) spiked in minipools	No. positive/ no. tested	% Positive
250.0	8/8	100
125.0	8/8	100
62.5	8/8	100
31.3	8/8	100
15.6	7/8	87.5
7.8	8/8	100
3.9	4/8	50
0.0	0/8	0

*Influenza (H5N1) standard was extracted from 9.6 mL of 96 pooled donor samples after centrifugation. Five microliters of 75-µL nucleic acid extract was analyzed. The 95% detection limit was 13.4 PFU/mL; the 50% detection limit was 4.8 PFU/mL.

Conclusions

As reported by AuBuchon et al. (*8*), NAT significantly increased the safety of blood products. At the German Red Cross, look-back examinations showed only 1 transfusion had transmitted HIV-1 (1998) after the introduction of NAT testing. Blood donor screening by NAT was made technically and financially feasible by creating minipools of up to 96 individual samples per pool. Roth et al. demonstrated an efficient enrichment for all tested viruses in plasma samples (*9*). In the absence of an infective donor, different concentrations of the new influenza genotype H5N1 were spiked into minipools of 95 samples. As shown in Table 2, the influenza (H5N1) subtype was detected by the generic influenza primers as well as by the influenza (H5N1)–specific primers when our routine minipool screening procedure was used. Sensitivity was expressed as PFU/mL and can be converted into viral genome copy number according the calculation of Yoshikawa et al. (*7*). Therefore, the analytical sensitivity was ≈804 geq/mL and 444 geq/mL for a generic influenza and for the influenza (H5N1) subtype, respectively.

After screening 10,272 samples by minipool NAT, none of the samples were found to be infected by influenza, which corresponds with the low EISS Index (European Influenza Surveillance Scheme index) of <20 during the study period (February–April, 2006) (*10*). An EISS index >80 is expected during an influenza epidemic, as was seen in 2005. Therefore, blood screening should be repeated during the next acute influenza season.

Table 2. Analytical sensitivity for avian influenza (H5N1) virus subtype for plasma samples*

PFU (H5N1) spiked in minipools	No. positive/ no. tested	% Positive
125.0	8/8	100
62.5	8/8	100
31.3	8/8	100
15.6	8/8	100
7.8	7/8	87.5
3.9	7/8	87.5
1.9	4/8	50
0.9	3/8	37.5
0.0	0/8	0

*Influenza (H5N1) standard was extracted from 9.6 mL of 96 pooled donor samples after centrifugation. Five microliters of 75-µL nucleic acid extract was analyzed. The 95% detection limit was 7.4 PFU/mL; the 50% detection limit was 2.5 PFU/mL.

Accepted incubation periods for influenza range from 2 to 10 days (*11,12*). As with other viruses, a viremic phase of infection can be assumed to precede clinical symptoms such as fever (*13,14*). Recently Chutinimitkul et al. (*15*) detected influenza (H5N1) virus (3,080 copies/mL) in the plasma of a 5-year-old boy, which indicates a viremic phase of influenza (H5N1) infection. Those donors may be infective, especially to immunosuppressed patients. In addition to quarantine of infected patients, treatment with antiviral drugs, and development of avian influenza vaccines, blood donors should be tested during a pandemic to avoid transfusion-transmitted infections. Our study demonstrates that NAT screening could be incorporated into blood testing without delay and that the influenza virus could be sufficiently enriched by centrifugation. Sensitivity of our influenza-screening method would have been sufficient to detect recently reported virus concentrations in plasma of infected persons (*15*). However, as with all minipool methods, infections can be transmitted to transfusion recipients on rare occasions because the viremia level in the donor is below the analytical sensitivity of the screening assay.

To reduce this risk, a selective infectious dose NAT strategy (e.g., triggering of infectious dose NAT testing when at least 1 viremic donation is collected per week with the standard minipool screening algorithm), as performed for West Nile virus (WNV) screening in the United States might be necessary. Implementation of WNV-NAT in the United States in 2003 interdicted well over 1,000 donations from persons infected with WNV and is a good example of successful implementation of NAT screening for emerging viruses.

The collective fight against new viruses such as severe acute respiratory syndrome virus, WNV, or influenza (H5N1) presents an immense challenge for the whole community, but new molecular-biologic methods offer opportunities to overcome this challenge. NAT screening tests are now available soon after the sequencing of new viruses. In the absence of a general pathogen inactivation method for all blood products (erythrocytes, platelets, and plasma), the NAT screening procedure allows testing for new viruses to ensure blood safety.

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Mr Hourfar is a research scientist at the German Red Cross blood donor service. His research interests include the molecular epidemiology of pathogens with special focus on blood safety.

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別紙様式第２－１

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 平成19年9月13日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	ﾃｸﾈﾁｳﾑ人血清ｱﾙﾌﾞﾐﾝ（^{99m}Tc）		研究報告の公表状況	Yang Yang, et al. Detecting Human-to-Human Transmission of Avian Influenza A (H5N1) Emerg Infect Dis Vol.13, No.9, September 2007;1348-53	公表国 米国	
販売名（企業名）	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）					

研究報告の概要

高病原性鳥インフルエンザA(HPAI)サブタイプH5N1は、東南アジアの広範囲に渡ってヒトからヒトへの感染による家族クラスターを引き起こした。このウイルス（または別の人畜共通インフルエンザウイルス）が、ヒトからヒトへの感染を維持する能力を得ている場合、世界的大流行を引き起こす恐れがある。
インドネシアのスマトラ北部とトルコ東部でHPAI（N5H1）感染した家族クラスターが、ヒトからヒトへの感染によるものであったかどうかを調べるため統計的手法を使用した。ヒトからヒトへの感染が起こると仮定し、地域basic reproductive number(R0)と二次感染の発生率(SARs)を推測する。解析の結果、トルコ(p=0.114)ではなくスマトラ（p=0.009）の家族クラスターで、ヒトからヒトへの感染した統計的証拠を見出した。スマトラでは家族内SAR（二次感染発生率）は0.29（95%信頼区間：0.15～0.51）であった。地域R0の推定下限値は1.14（95%信頼区間:0.61～2.14）であった。HPAI（H5N1）監視効果、封じ込め対応、そして実地評価には、ウイルス株の大流行の可能性阻止と監視が不可欠である。

報告企業の意見	今後の対応
高病原性トリインフルエンザ（H5N1）が「人から人へ感染した」ことを、統計的手法によって証明した初めての報告である。本報告は、新たに判明した感染経路に関するもの且つ重大な感染症に関するものと判断する。	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するものではなく、現時点で特に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。 本研究報告では、ウイルスが伝播するためにはヒトとの極めて密接な接触が必要だったとし、簡単に伝播するわけではないことを示唆しているが、このウイルスがヒトからヒトへの感染を維持する能力を有したかどうかは不明と報告しており、今後も同様の情報に注意し収集する必要があると考える。

使用上の注意記載状況・その他参考事項等

特になし

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