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研究報告の概要	使用上の注意記載状況・その他参考事項等
ヒトパルボウイルス B19（B19V）感染症は，溶血または赤血球生成不全症候群などのある血液病患者にとって重篤な感染症となり得る。血漿製剤とは対照的に，成分輸血による B19V 感染症例報告は稀であるが，いずれの研究においても，B19V DNA 陽性成分輸血の受血者への感染率は体系的に測定されていない。本研究では，供血者および受血者由来の保存血液検体中の B19V DNA 量を高感度のリアルタイム定量 PCR アッセイにより測定し，B19VDNA 陽性成分（赤血球製剤 77%，全血由来血小板製剤 13%，新鮮凍結血漿製剤 10%）の成分輸血による B19V 感受性（輸血前に B19V IgG 抗体陰性）受血者の B19V 感染率を評価した。実際には B19VDNA 陽性であった 105 例の供血者由来の B19VDNA 陽性成分 112 検体が輸血された，輸血前 B19VIgG 抗体保有率 78%の 112 人の患者群（２４名が感受性受血者）について調査を行い，IgG あるいは IgM への抗体陽転，もしくは B19V DNA の新規検出をもって，B19V 感染成立と定義した。その結果，B19V DNA 量が 10^6 IU/mL 以下の成分輸血を受けた感受性受血者 24 例への B19 感染伝播は見られなかった（95%信頼区間，11.7%）。B19V DNA 量が 10^{10} IU/mL 以上の成分輸血を受けた非感受性受血者（輸血前 B19V IgG 抗体陽性）1 例で既往反応が認められた。本研究では，B19V DNA 量 10^6 IU/mL 以下の成分輸血による感染伝播は起こらない，また，もし感染が起こったとしても，感染率が 50%以上を示す多くの輸血感染症（HIV，HCV など）と比較すると，B19V 感染はまれな事象であることが示された。	BYL-2010-0397

報告企業の意見	今後の対応
本研究では，受血者の状態による評価はなされておらず，また調査の規模つまり，評価のターゲットである感受性受血者数が少ないためこれらを加味した研究がという問題が残されてはいるが，ヒトパルボウイルス B19 の DNA 量について，10E6IU/m l という安全域の目安が示された。なお，弊社のコージネイト FS の製造工程培地で使用されている血漿分画成分に使用されるミニプール血漿においては，ヒトパルボウイルス B19 に対する NAT を実施しており，10E5 IU/mL 以上が確認された場合は，そのミニプール血漿は製造工程から除去している。現在の科学水準では，ヒトパルボウイルス B19 を確実に不活化する方法は存在しないため，感染リスクを完全に排除することはできないが，伝播の可能性は非常に低いと考える。	現時点で新たな安全対策上の措置を講ずる必要はないと考えるが，今後ともウヒトパルボウイルス B19 の感染に関する情報収集に努める。

A linked donor-recipient study to evaluate parvovirus B19 transmission by blood component transfusion

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Parvovirus B19V infection can be a serious infection for hematology patients with underlying hemolysis or compromised erythropoiesis syndromes. Although case reports of B19V transmission by blood component transfusion (as contrasted to manufactured plasma derivatives) are rare, no studies have systematically determined a rate of transmission to recipients transfused with B19V DNA–positive components. We used a linked donor and recipient repository and a sensitive, quantitative B19V DNA polymerase chain reaction (PCR) assay to assess such transmission in B19V-susceptible (ie, anti-B19V immunoglobulin G [IgG] negative) recipients. We assessed 112 B19V DNA–positive components from 105 donors (of 12 529 tested donations) transfused into a population of surgical patients with a pretransfusion B19V IgG seroprevalence of 78%. We found no transmission to 24 susceptible recipients from transfusion of components with B19V DNA at concentrations less than 10^6 IU/mL (upper 95% confidence interval, 11.7%). We found an anamnestic IgG response in one pretransfusion seropositive recipient transfused with a component containing greater than 10^{10} IU/mL B19V DNA. These findings show either that transmission from components with less than 10^6 IU/mL does not occur, or, if it does, it is an uncommon event. These data do not support the need to routinely screen blood donations with a sensitive B19V DNA nucleic acid assay. (Blood. 2009;114:3677-3683)

Introduction

There have been multiple reports of parvovirus B19 (B19V) transmission by pooled plasma products, including factor VIII concentrate and solvent-detergent–treated pooled plasma, documented by recipient seroconversion in asymptomatic cases or, less frequently, by clinical diagnosis of B19V-related disease in association with positive B19V test results.[1-5] These cases, combined with the potential for very high B19V DNA concentrations (up to 10^{12} IU/mL) in plasma donations[4] and the relative resistance of B19V to inactivation methods,[4,6] have led to B19V DNA testing of plasma donations to ensure that manufacturing plasma pools destined for plasma derivatives have a B19V DNA concentration less than or equal to 10^4 IU/mL, a limit proposed by the Food and Drug Administration (FDA).[7-9] The same limit for this so-called "in process testing" is a European regulatory requirement for anti-D immunoglobulin (Ig) preparations and plasma treated for virus inactivation.[10] To achieve this B19V DNA concentration in the final plasma pool, B19V DNA screening of the plasma donations used to make the pool is performed using assays (applied in minipool format) with the ability to detect approximately 10^6 IU/mL in an input unit of plasma.[8]

To date, no B19V transmissions from pooled plasma products have been documented when less than 10^3 to 10^4 IU/mL B19V DNA is present in an infused product.[3,4,11-13] The reason for this lack of infectivity is not completely understood. It may be due to an inadequate amount of infused infectious virions, a neutralization effect from B19V antibody present in other plasma units in the plasma pool, or a combination of these factors. Recipient factors may also play a role because it has been reported that B19V antibody is protective against B19V reinfection, and most of the adult population is B19V seropositive as a result of previous infection.[13]

Although concern for transmission of B19V from pooled plasma products has resulted in B19V DNA screening of input plasma donations, less is known about the potential for B19V transmission by transfusion of individual blood components (eg, red cells, platelets, plasma). There are only 4 published clinical cases of B19V transmissions from blood component transfusion (3 from red cells and 1 from platelets).[14-17] An additional asymptomatic case has been reported from a recent prospective study of transfusion-transmitted viral infections.[18] In contrast, 2 studies have reported a small number of negative results when patients transfused with B19V DNA–positive components were evaluated for laboratory markers of B19V infection.[19,20] Nevertheless, given the tropism for[21] and potential pathophysiologic effects of B19V infection on erythroid precursor cells,[22] concern remains for potential deleterious outcomes in frequently transfused hematology patients with underlying hemolysis or compromised erythropoiesis syndromes.[13]

Because the sensitivity of B19V DNA assays has improved, B19V DNA prevalence in blood donors has been shown to be

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higher than initially documented. B19V DNA is detectable in 0.5% to 0.9% of blood donations, with most showing relatively low DNA concentrations (< 100-1000 IU/mL).[23-25] In addition, it has become established that B19V infection is often persistent.[25-27] Thus, some donors may continue to donate for many years with B19V DNA (and potentially infectious virions) in their blood. These observations suggest that the potential for recipients to be exposed to low levels of B19V DNA from blood component transfusion is greater than previously thought.

To our knowledge, there have been no large-scale donor/recipient-linked transfusion-transmission studies to evaluate the rate of B19V transfusion transmission. Although it has been assumed by extrapolation from pooled plasma transfusions that single unit blood components with low-level B19V DNA should be noninfectious, this remains speculative because the mechanism of protection in the pooled plasma setting has not been established and may not apply to single unit transfusions.[12,13]

We undertook this present study to systematically evaluate whether transfusion of blood components with low or moderate levels of B19V DNA (defined as < 10^6 IU/mL) transmits infection to B19V-seronegative susceptible recipients.

Methods

Source of donor and recipient samples

Tested specimens were from the National Heart, Lung, and Blood Institute (NHLBI) Retrovirus Epidemiology Donor Study Allogeneic Donor and Recipient (RADAR) repository, which was established to investigate possible transfusion-transmitted infections and which has been described in detail in a previous publication.[28] Repository specimens were collected from 2000 through 2003 by blood centers and selected hospitals at 7 geographically dispersed US locations. Repository specimens consisted of 2 frozen 1.8-mL plasma aliquots and a 1.5-mL sample of frozen whole blood.

All enrolled donors and recipients gave informed consent for frozen specimen storage and for subsequent specimen testing for possible transfusion-transmissible infections, in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board of each participating institution.

The linked portion of this donor-recipient repository contains pretransfusion and/or peritransfusion specimens and follow-up specimens, collected at a 6- to 12-month interval, from 3575 enrolled recipients. It also contains 13 201 donation specimens given by 12 408 distinct donors that were transfused to these recipients. The RADAR enrollment procedure targeted recipients with expected high 1-year survival rates; 88% were cardiac or vascular surgical patients, and the median recipient age was 68 years (range, 59-74 years). Recipients were not evaluated for coexisting immunosuppression, but this is considered unlikely given the primary diagnoses. The mean number of RADAR donation exposures per recipient was 3.9. The distribution of component types transfused was 77% red cells, 13% whole-blood–derived platelet concentrates, and 10% fresh-frozen plasma (FFP). In addition to receiving components with a stored donation specimen in the RADAR repository, these recipients also received a mean of 3.1 components not linked to stored RADAR donations.

The RADAR repository also contains 99 906 specimens from blood donations that were not transfused to enrolled RADAR recipients; this supplementary repository served as a sample source during the assay validation and donor prevalence phase of the study, which has previously been reported.[24]

Selection and testing of donations

All RADAR donations transfused to enrolled recipients were tested for B19V DNA, provided there was adequate specimen volume available.[24] Donations found reactive on the B19V DNA assay were subjected to DNA confirmatory and quantitative testing; confirmed positive donations were also tested for B19V IgG and IgM.

Selection and testing of recipients

Cases were recipients who were transfused with one or more B19V DNA–positive components. Control recipients were selected to measure the background rate of new infection as a result of factors other than transfusion of a B19V DNA–positive RADAR unit (ie, community-acquired infection in the 6- to 12-month follow-up interval or a transfusion-acquired infection from a B19V DNA–negative RADAR unit or a nontested, non-RADAR unit). A 1:2 case-control design was used to select control recipients fulfilling the following criteria: all RADAR units received by the recipient were B19V DNA negative, enrollment occurred at the same participating center in approximately the same time frame (to control for community-acquired infection), and age was within 10 years of the case recipient. Using this control selection algorithm, we established that all controls met preestablished age and center criteria, and 94.4% received their transfusion within 11 days of their matched recipient.

Enrollment specimens from all case and control recipients were tested for B19V IgG. Before knowledge of B19V IgG enrollment results, posttransfusion follow-up specimens from all cases and controls were tested for B19V IgG, IgM, and DNA (see "Assay methods"). A positive B19V DNA or IgM result on the follow-up specimen triggered additional testing of the enrollment specimen for these analytes.

For analysis, case and control recipients with negative B19V IgG results before transfusion were subsequently classified as B19V susceptible, and those with positive results were classified as B19V nonsusceptible.

Protocol for evaluating transfusion-transmission

B19V transmission was defined as seroconversion to IgG or IgM or new detection of B19V DNA. Because our previous experience with B19V antibody testing has shown that specimens near the cutoff could show fluctuating results on different test runs, we required that seroconversion be independently shown by 2 laboratories.

Assay methods

B19V DNA PCR assay. The B19V DNA polymerase chain reaction (PCR) assay was originally developed by Chiron Corporation and subsequently refined through collaboration between Chiron and Blood Systems Research Institute (BSRI). We previously reported data on assay performance on 5020 plasma samples from the unlinked donor portion of the RADAR repository.[24] The assay had a 50% limit of detection (LOD) of 1.6 IU/mL (95% confidence interval [CI], 1.2-2.1 IU/mL) and a 95% LOD of 16.5 IU/mL (95% CI, 10.6-33.9 IU/mL). We determined that the assay could be used as a quantitative as well as a qualitative assay; because quantitation might not be precise at the lower LOD, we categorized all specimens with quantitative DNA values of greater than 0 but less than 20 IU/mL as having a value of less than 20 IU/mL.

The assay, performed at BSRI, included a magnetic-bead B19V DNA capture step followed by a TaqMan real-time PCR assay targeting the VP1 region of the genotype 1 B19V genome. The assay was subsequently validated as detecting genotype 2 but does not detect genotype 3, which has been identified in Africa but which is very rare outside that continent.[20] An internal control sharing homologous primer region sequences but with a different internal probe binding sequence as the viral target was included in each assay tube. All captured target DNA from 0.5 mL input plasma and the spiked internal control was amplified in a single PCR reaction by using the same primer pair. Amplification and detection occurred in a 96-well optical plate by using dual-plexed TaqMan PCR technology. B19V target and internal control DNA were detected and distinguished by fluorophore-tagged sequence-specific probes. Each plate contained 2 known positive, 2 blinded negative, and 2 blinded positive controls and up to 90 study specimens. A more detailed assay description is provided in the previous publication.[24]

Because the chosen assay cutoff of a cycle threshold (C_T) of less than 40 was designed to maximize assay sensitivity, an algorithm was developed

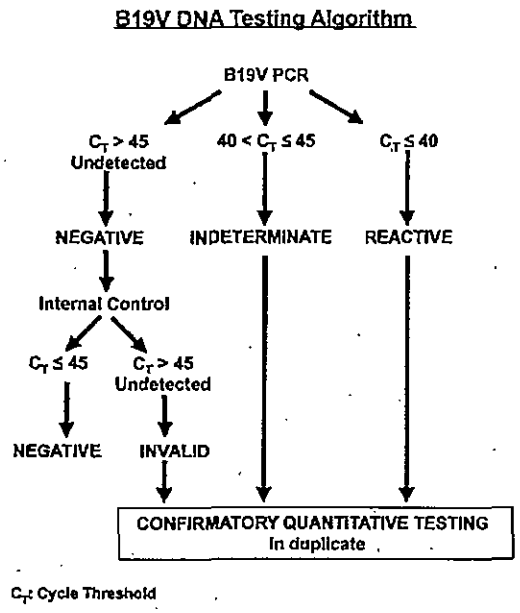

Figure 1. B19V DNA testing algorithm.

for final test interpretation so as to avoid classifying nonspecific reactivity on a single assay run as a confirmed positive result (Figure 1). All initially positive, indeterminate, and invalid specimens were retested in duplicate on plates that included quantitative run standards by using 2 separate 0.5-mL subaliquots subjected to the full extraction, amplification, and detection procedure. This testing served both as confirmation and quantitation. Final interpretation was based on the results of the 3 assays (ie, the initial screening assay and the duplicate repeat assays). Specimens were classified as B19V DNA positive if at least 2 of 3 tests showed reactivity at a C_T less than 40.

For determining DNA concentration, duplicate quantitative run standards (containing B19V DNA at 10^0 to 10^6 IU/mL) were placed on each plate, and quantitative results were determined by comparing the specimen C_T to the C_T of the known standards on the same test run.[24] The assigned quantitative value for each specimen was the average of the duplicate quantitative assays (including zero for a negative test result). Specimens with low C_T values (< 30) were diluted 1:10 and 1:100 and then run in triplicate at each dilution. The quantitative result was the average of the 3 test results at the most appropriate dilution adjusted by the dilution factor.

Serologic assays. Testing for B19V IgG and IgM was directed against a recombinant VP2 protein and was performed in duplicate by using FDA-cleared test kits (Biotrin) according to the manufacturer's instructions. Testing was conducted at BSRI and, for a large subset of samples, was repeated at a Center for Biologics Evaluation and Research/Food and Drug Administration (FDA) laboratory (Bethesda, MD). If results fell into the equivocal zone, the assay was repeated in duplicate on a new aliquot, and this repeat result was taken as the final result for the specimen.

Quantitative B19V IgG testing was performed by using a standard curve dilutional analysis method with the World Health Organization First International Standard for B19V serum IgG (93/724) obtained from the National Institute for Biological Standards and Control.[29] This testing was applied to enrollment and follow-up specimens of B19V IgG–positive ("nonsusceptible") recipients who had been transfused with the 5 highest titer B19V DNA components identified through donor testing.

Statistical methods

On the basis of a review of donor B19 viremia and recipient B19V serologic data from phase 1 of this study,[24] we determined that testing of the linked donor and recipient RADAR repository specimens would have sufficient statistical power such that a finding of zero documented transmissions to susceptible recipients would indicate with 95% confidence that the true B19 transfusion–transmission rate was between 0% and 25%. In this current study, StatXact (Cytel) was used to generate upper 95% confidence limits based on zero observed infections.[30] The upper confidence limit for transmission was calculated as a one-sided exact 95% confidence interval for the difference between the infection rate among susceptible cases and susceptible controls, using StatXact (Cytel).[30]

Results

Of the 13 201 linked blood donation repository specimens, 12 529 (95%) had adequate volume for testing. B19V DNA was detectable in 105 donations for a prevalence of 0.84% (95% CI, 0.68%-1.00%). As shown in Table 1, 53%, 71%, and 93% of these donations had B19V DNA concentrations below 20, 100, and 1000 IU/mL, respectively. The 2 donations with DNA concentrations greater than 10^6 IU/mL were negative for B19V-specific IgM and IgG, whereas B19V IgG was detectable in 96% and B19V IgM in 28% of the evaluable remaining B19V DNA–positive donations.

These 105 B19V DNA–positive donations came from 103 donors, 2 of whom gave positive donations on 2 occasions. The 105 positive donations resulted in the transfusion of 112 positive components to enrolled recipients. Four recipients received multiple DNA-positive components such that a total of 107 distinct recipients were transfused with one or more DNA-positive components. Table 2 provides a description of the DNA-positive components transfused to recipients, classified by the DNA concentration of the component, by whether the recipients were susceptible to B19V infection (ie, B19V IgG negative on their enrollment

Table 1. Quantitative B19V PCR and antibody results on confirmed positive donations

B19V DNA concentration, IU/mL, in donation	No. of B19V DNA–positive donations	No. (%) B19V IgM and IgG positive	No. (%) B19V IgM negative, IgG positive	No. (%) B19V IgM negative and IgG negative
Less than 20	56	2 (4%)	52 (93%)	2 (4%)
20 to less than 100	19*	5 (28%)	13 (72%)	0
10^2 to less than 10^3	23	18 (78%)†	2 (9%)	1 (4%)
10^3 to less than 10^4	4	4 (100%)	0	0
10^4 to less than 10^5	0	0	0	0
10^5 to less than 10^6	1	0	0	1 (100%)
Subtotal	103*	29 (28%)	67 (66%)	4 (4%)
More than 10^6	2	0	0	2
Total	105‡	29	67	6

The prevalence of B19V DNA–positive donations in 12 529 tested donations was 0.84%.
*One donor was not tested for B19V antibody; percentages have been calculated eliminating that donor from both the numerator and the denominator.
†Two donors were IgM equivocal and IgG positive.
‡The 105 B19V DNA–positive donations came from 103 donors, 2 of whom gave positive donations on 2 occasions.

Table 2. Transfusion of B19V DNA-positive components to recipients

B19V DNA concentration, IU/mL, in donation	No. of B19V DNA-positive donations	No. of B19V DNA-positive components transfused to susceptible recipients*				No. of B19V DNA-positive components transfused to nonsusceptible recipients				Total no. of B19V DNA-positive components transfused
		Red cells	Platelets	Plasma	Subtotal	Red cells	Platelets	Plasma	Subtotal	
Less than 20	56	15	0	1	16	33	6	5	44	60
20 to less than 100	19	3	0	0	3	9	5	3	17	20
10^2 to less than 10^3	23	3	1	0	4	16	3	2	21	25
10^3 to less than 10^4	4	0	0	1	1	2	0	1	3	4
10^4 to less than 10^5	0	0	0	0	0	0	0	0	0	0
10^5 to less than 10^6	1	0	0	0	0	1	0	0	1	1
Subtotal	103	21	1	2	24	61	14	11	86†	110†
More than 10^6	2	0	0	0	0	1	1	0	2	2
Total	105	21	1	2	24	62	15	11	88†	112†

*All B19V DNA-positive units transfused to susceptible recipients contained B19V-specific IgG.
†For 7 B19V DNA-positive donations, more than 1 component was transfused; also 4 nonsusceptible recipients received more than 1 positive component.

specimen), and the type of blood component. As per RADAR repository design, the majority (74%) of transfused DNA-positive components were red cell concentrates. Twenty-four of the 112 components (21%) were transfused into susceptible recipients. Among the 214 control recipients (2 controls selected per case), a very similar percentage (20%) were susceptible. Six of the 7 DNA-positive components with the highest concentrations were transfused to nonsusceptible recipients; these included all 3 components with DNA concentrations greater than 10^5 IU/mL.

The primary analysis of transfusion transmission was restricted to the 24 susceptible (B19V IgG negative) cases (21 transfused with red cells) and the 42 susceptible controls. There were no B19V infections observed in these 66 susceptible recipients based on the absence of B19V IgG, IgM, and DNA in the follow-up specimens. Thus, the transmission rate was 0% in both cases and controls, with an upper 95% CI of 11.7% in cases and 6.9% in controls. The transfusion-transmission rate was therefore estimated at 0.0% [0.0% (cases) − 0.0% (controls)], with an upper 95% CI of 11.7%.

Although IgG seroconversion could not be used as a criterion for establishing transfusion-transmission in nonsusceptible subjects (those with preexisting B19V IgG), the criteria of newly developed B19V DNA or IgM were still applicable. There were no such findings in case recipients. However, one IgM seroconversion was identified in a B19V IgG–positive (nonsusceptible) control recipient who remained DNA negative. Because this recipient was transfused with only 2 DNA-negative red cell units (and no non-RADAR units), it is likely that the IgM seroconversion represents a false-positive result or possibly a new community-acquired infection. Testing also identified B19V DNA in follow-up specimens of 3 other control recipients. However, testing of their enrollment specimens indicated that B19V DNA was present before transfusion at approximately the same concentration in all 3 cases. Furthermore, their enrollment and follow-up specimens were positive for B19V IgG antibodies. Thus, this pattern indicated persistent B19V infection (existing before receiving RADAR transfusions) rather than recent B19V acquisition.

To further evaluate whether transfusion with B19V DNA–containing units elicited an immune response in subjects with preexisting B19V IgG, we performed quantitative B19V IgG testing of enrollment and follow-up specimens of the 5 recipients who were B19V IgG positive at enrollment and who received the highest titer DNA-positive components, reasoning that these would provide the maximal stimulus for such an immune response. Pretransfusion B19V IgG levels were highly variable, ranging from 7 to 165 IU/mL. As seen in Table 3, 1 of the 5 recipients, who received the highest titer component (at a B19V DNA concentration of 2.9×10^{10} IU/mL or a total dose of $\sim 5.8 \times 10^{11}$ IU in the 20 mL plasma contained in the red blood cell component), showed a 4-fold increase in B19V IgG titer. This recipient had a relatively low pretransfusion titer of B19V IgG (15 IU/mL). Of the other 4 recipients, 1 showed a 2-fold increase, 2 had unchanged titers, and 1 showed an almost 2-fold decrease.

Discussion

In this study we identified donations that had a potential marker of B19V infectivity (ie, B19V DNA) through retrospective screening of blood donations and subsequently tested recipients of components from these donations for the development of new B19V infection. Our approach was designed to systematically determine a rate of transmission from all units with this potential infectivity marker and to establish either the presence or absence of transmission when it was known that a susceptible (ie, B19V IgG negative) recipient was transfused with a potentially infectious (ie, B19V DNA positive) unit. This study design is in contrast to most other B19V studies in which investigations were structured to prove that transmission occurred in a particular case.

On the basis of our finding of nontransmission in 24 evaluable susceptible (B19V seronegative) recipients of components with a B19V DNA concentration less than 10^6 IU/mL, we conclude that the rate of transmission from such components ranges from 0% to 11.7% (which is the upper 95% confidence bound); thus, either transmission from such components does not occur, or, if it does, it is a relatively uncommon event in comparison to most other transfusion-transmissible viruses in which infection rates exceed 50% (eg, HIV, HCV).[31]

Table 3. Antibody quantitation studies in recipients transfused with components with the highest B19V DNA concentrations

Transfused component results		Recipient results	
B19V DNA concentration, IU/mL, in donation	B19V IgM/IgG status	Enrollment B19V IgG titer, IU/mL	Follow-up B19V IgG titer, IU/mL
2.9×10^{10}	−/−	14.9	61.1
8.2×10^{7}	−/−	53.5	33.4
4.3×10^{5}	−/−	37.5	40.2
8.6×10^{3}	+/+	7.6	15.2
1.8×10^{3}	+/+	165.1	157.9

*One recipient who received a component with a DNA concentration of 3.1×10^3 IU/mL (which was also positive for B19V IgM and IgG) was not included in this table because the enrollment and follow-up specimens were both B19V IgG negative.

Our study is the first to evaluate transmission in multiple recipients who do not have preexisting B19V IgG and hence do not have this mechanism for potential protection against acquiring B19V infection. In a study from Africa, there was a single documented case of lack of B19V transmission to a susceptible pediatric recipient transfused with a red cell unit that had a B19V DNA concentration of 6×10^2 IU/mL in the presence of B19V IgG.[20] There are somewhat more data about the lack of transmission to recipients with preexisting B19V IgG. In a study conducted in an adult hematology service, 6 adult recipients with hematologic malignancies (5 of whom underwent stem cell transplantation) were identified as transfused with blood components that were retrospectively found to contain B19V DNA at less than 10^6 geq/mL; in 4 of 5 evaluated cases, the DNA-positive component also contained B19V IgG. Each recipient was B19V DNA negative when tested 3 to 18 days after transfusion,[19] and none showed clinical symptoms of B19V infection on retrospective chart review.[19]

The mechanism to explain lack of transmission to susceptible recipients by B19V DNA–containing units is unknown but could be related to the lack of a large enough inoculating dose of B19 virions to establish infection. This could be due to the ratio between infectious dose and virion number (which is not known), the low levels of transfused intact and/or replication competent virions in units with low DNA concentrations, or neutralization of otherwise infectious virions either by antibody in the transfused unit or by passively transfused antibody from other units.[12] In support of the latter explanations, we note that all DNA-positive units transfused to susceptible recipients in our study contained B19V-specific IgG. In addition,it is highly probable that all recipients of B19V DNA–containing components received some additional blood components with B19V IgG; this is based on our previous findings that 73% of donors who contributed to the RADAR repository had B19V IgG[24] and that RADAR recipients were transfused with an average of 7 blood components.[28]

Our negative transmission findings are consistent with previous publications that have shown that high plasma concentrations of B19V DNA are required for transmission in the setting of transfused pooled plasma products. The minimal infectious dose of B19V DNA documented to cause a symptomatic B19V infection in a recipient of factor VIII concentrate devoid of B19V IgG was 2×10^4 IU based on the infusion of 3 vials of a product with a DNA concentration of 6.5×10^3 IU/vial (ie, 1.3×10^3 IU/mL when each vial was reconstituted in a 5-mL volume).[3] Furthermore, we are aware of only one comprehensive quantitative transmission study of pooled plasma products manufactured from multiple donations.[11,32] That study, conducted approximately 10 years ago, was an open-label phase 4 trial of pooled plasma, solvent detergent-treated (PLAS + SD produced by Vitex, now defunct). One hundred B19V-seronegative volunteers were infused with product from 17 different manufacturing lots. Of 19 subjects who received the product from 3 lots that contained at least 2×10^9 geq B19V DNA (ie, 200 mL product infused at $> 10^7$ B19V DNA geq/mL), 18 seroconverted and 17 showed B19 viremia. Although the investigators expressed their results in geq/mL, it has subsequently become established that for B19V, an IU and a geq are approximately equivalent. In contrast, there were no seroconversions in 81 subjects who received product from 1 of 14 lots containing less than 10^4 geq/mL B19V DNA; however, the investigators did not more precisely quantitate the amount of B19V DNA in these nontransmitting lots.

In our study, which was designed to systematically study transmissibility from B19V DNA–positive units with less than 10^6 IU/mL, we transfused only 2 components with high B19V DNA concentrations ($> 10^7$ IU/mL) but were unable to directly evaluate their transmissibility in susceptible recipients, because both were transfused to recipients with preexisting B19V IgG. We used quantitative B19V antibody testing to investigate whether exposure to this very high B19V DNA concentration could stimulate the recipient's immune system to respond. Although not definitive, a 4-fold boost in B19V IgG in the follow-up specimen from one of these recipients suggests that a component with very high B19V DNA concentration ($\sim 5.8 \times 10^{11}$ IU B19V DNA infused) can result in an anamnestic response (implying transient active viral replication) in a previously exposed recipient when the pretransfusion antibody titer is relatively low (15 IU/mL in this recipient). Our results are consistent with similar 4-fold B19V IgG increases which were reported 1 month after transfusion in 2 of 2 B19V IgG–positive volunteers who remained asymptomatic after transfusion of 200 mL PLAS + SD at a B19V DNA concentration of 1.6×10^8 IU/mL.[32] In addition, in the previously described study of adult hematology patients, there was also one B19V IgG–positive recipient of a red blood cell unit containing 2.2×10^6 geq/mL of B19V DNA; this recipient was positive for B19V DNA at posttransfusion day 5, negative when retested on day 35, and asymptomatic for B19V infection on chart review; B19V IgG titer was not reported.[19]

Despite the large size of our linked donor–recipient repository, the use of a very sensitive B19V DNA assay, and a rigorous testing algorithm, this study was subject to several limitations. The collection of recipient follow-up specimens 6 to 12 months after transfusion limited the laboratory techniques that we could use to diagnose new B19V infection. In addition to our primary assessment of the development of new B19V IgG formation, we also tested for new appearance of B19V IgM and B19V DNA. However, the natural history of acute B19V infection predicts that both of these markers would probably no longer be detectable at the time our follow-up specimens were collected, unless the recipient had developed a persistent infection.[13,33] Our study was also limited because most recipients (78%) of B19V DNA–positive units were B19V IgG positive before transfusion and thus presumably were partially or totally protected against B19V reinfection. This limited the statistical power of our negative result such that the upper 95% CI could not rule out a transmission rate as high as 11.7%. Furthermore, most of the 24 susceptible recipients received components with very low B19V DNA concentrations (< 20 IU/mL). We identified only 5 transfused components with DNA concentrations between 10^3 and 10^6 IU/mL; 4 of these were B19V IgM and IgG positive, and one of these (DNA level of 4.3×10^5 IU/mL) lacked B19V antibody. Furthermore, only one of these components, a plasma unit containing a total infused dose of approximately 7×10^5 IU in the presence of B19V IgG, was transfused to a susceptible recipient. Similarly, although we identified 45 transfused components with B19V DNA concentrations between 20 and 1000 IU/mL, only 7 were transfused to susceptible recipients. Finally, although we obtained questionnaires from recipients at the time of follow-up (6-12 months after transfusion) and none of the recipients had been diagnosed with B19V disease, we were unable to definitively assess nonspecific symptoms that can occur with B19V infection at such a long interval after transfusion.

We expressed our findings as the rate of transmission in susceptible recipients because this allowed us to extrapolate our findings to other transfused recipient populations; ie, it allowed us to calculate a per unit risk. This per unit risk in our older surgical recipients can then be applied to populations with a higher susceptibility rate (eg, fetuses undergoing intrauterine transfusion, young patients with sickle cell anemia or thalassemia, patients with

congenital or acquired hypogammaglobulinemia), based on the assumption that the equivalent dose of B19V transfused into a B19V IgG–negative hematology or surgical patient will result in productive infection (ie, viral replication) at the same rate. In our opinion, it is unlikely that the infectivity of a B19V DNA–positive transfused unit will be related either to the underlying disease or to the overall immune status of a B19V seronegative recipient, even though it is well accepted that the clinical manifestations of a B19V infection will be influenced by such host factors (ie, if infected with B19V, an immunosuppressed patient or one with an underlying hemolytic syndrome might have a worse clinical outcome).[7]

We can also analyze our data on a population-wide basis; looked at in this way, we did not detect any cases of definite B19V transmission (with the exception of the one possible case of an anamnestic immune response) after the transfusion of blood components from 12 529 B19V DNA–tested donations into a recipient population with a pretransfusion B19V IgG prevalence of 78%.

As part of this study, we also generated a large body of blood donor data. We found that B19V DNA prevalence in 12 529 tested donations was 0.84%, consistent with our previous report of 0.88% in 5020 donation samples from the same RADAR repository and with higher end estimates in literature.[23-25] The large majority of our DNA-positive donations had low or very low DNA concentrations (53%, 71%, and 93% below 20, 100, and 1000 IU/mL, respectively), consistent with the interpretation that the increased DNA prevalence found in recent donor studies is due to the use of more sensitive nucleic acid testing assays. In contrast to the high rate of overall DNA detection, our rate of detection of high-titer DNA positives ($> 10^6$ IU/mL) was approximately 1 in 6000, consistent with both the newer and older literature.[7,34,35] These high-titer units are known to occur in the acute phase of B19V infection; thus, they lack both B19V IgG and IgM antibody as was the case in this study.[31] In contrast, 96% of the remaining DNA-positive donations were B19V IgG positive, which is the expected result in resolved or persistent infection.[35,36]

Current practices for blood donor screening for B19V in developed countries are almost exclusively confined to testing plasma designated for fractionation for the presence of high B19V DNA concentrations.[8,13] There has been recent debate about whether such screening should also be applied to transfused blood components; this is currently not done because of the lack of demonstrated adverse clinical outcomes from B19V infection in blood component recipients and the considerable expense of such testing. We are aware of only one country, Germany (which also performs blood testing for Austria), in which some blood banks currently conduct B19V DNA screening of blood donations and use the results to release blood components for transfusion.[35]. Their testing is conducted in pools of 96 samples with an assay that can reliably detect units with B19V DNA greater than 10^5 IU/mL. Other German blood banks conduct B19V DNA testing retrospectively after the red cell component has been transfused.[35] In a recent abstract, preliminary data indicate that B19V transmission (documented by a positive B19V DNA test in the transfused recipient) from retrospectively tested red cell components occurred when the B19V DNA concentration was greater than 10^5 IU/mL but not when the concentration was below this threshold.[37]

Our study results confirm that, if prospective, real-time B19V DNA blood donor screening were to be performed, the assay sensitivity used in Germany (ie, detection limit $< 10^5$ IU/mL) is reasonable in that it ensures recipient safety while preventing unnecessary discard of a much larger number of blood components. Our findings do not support the need to use more-sensitive B19V DNA nucleic acid screening assays. In conclusion, our data indicate that blood components with B19V DNA less than 10^6 IU/mL (almost all of which contain B19V-specific antibody) are unlikely to transmit B19V infection.

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Authorship

Contribution: S.H.K., S.A.G., and M.P.B. designed the study; T.-H.L., L.H.T., D.S.T., and M.-y.W.Y. supervised laboratory testing; S.H.K., S.A.G., M.P.B., K.S.S., D.S.T., and H.Q. analyzed data; and S.H.K., S.A.G., M.P.B., and M.-y.W.Y. wrote the manuscript.

Conflict of interest disclosure: The authors declare no competing financial interests.

A complete list of the members of the NHLBI REDS-II appears in the supplemental Appendix (available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

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研究報告の概要

○慢性疲労症候群において新規レトロウイルスXMRVは検出されなかった
背景:2009年10月、米国の慢性疲労症候群(CFS)患者101名のうち68名が、異種指向性ネズミ白血病ウイルス関連ウイルス(XMRV;以前に前立腺がんとの関連性が示された新規ガンマレトロウイルス)に感染していることが報告された。本知見が確認された場合、世界中で数百万人が罹患し、身体機能を奪う当該疾患の理解と治療に多大な影響を及ぼすであろう。我々は、英国のCFS患者がXMRVキャリアであるかどうかを調べた。
方法:本試験のCFSコホート患者は、検査により他の器質性疾患を除外されており、CFSのCDC基準を満たしていた。CFS患者186名の血液検体から抽出したDNAについて、特異的オリゴヌクレオチド・プライマーを用いたnested PCRによる、XMRVプロウイルスおよび関連性の高いネズミ白血病ウイルス(MLV)のスクリーニングを行った。DNAの内部コントロールのため、細胞βグロビン遺伝子を増幅した。陰性対照(水)と陽性対照(XMRV感染分子クローンDNA)を含めた。βグロビン遺伝子を186名全員の検体で増幅したが、XMRVもMLV配列も検出されなかった。
結論:英国のCFS患者由来DNAからは、XMRVまたはMLV配列は増幅されなかった。本試験では英国のXMRVがCFSに関連する証拠を見つけなかったが、北アメリカとヨーロッパ間でのXMRV感染の一般有病率に集団差がある可能性があり、米国の2グループが前立腺がん組織にXMRVを発見したにもかかわらずヨーロッパの2試験で発見されなかったのは、このためであるかもしれない。

報告企業の意見	今後の対応
英国の慢性疲労症候群患者186名の血液検体から、新規レトロウイルスXMRVのDNAは検出されなかったとの報告である。 XMRVはマウス白血病ウイルスと類縁な脂質膜を持つ大型RNAウイルスである。この性状からは本製剤の製造工程でウイルス不活化・除去されると期待されることから、本製剤の安全性は確保されていると考える。	注目すべきウイルスとして今後も引き続き、新たなウイルス等に関する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

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

(15)

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PLoS one

Failure to Detect the Novel Retrovirus XMRV in Chronic Fatigue Syndrome

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Abstract

Background: In October 2009 it was reported that 68 of 101 patients with chronic fatigue syndrome (CFS) in the US were infected with a novel gamma retrovirus, xenotropic murine leukaemia virus-related virus (XMRV), a virus previously linked to prostate cancer. This finding, if confirmed, would have a profound effect on the understanding and treatment of an incapacitating disease affecting millions worldwide. We have investigated CFS sufferers in the UK to determine if they are carriers of XMRV.

Methodology: Patients in our CFS cohort had undergone medical screening to exclude detectable organic illness and met the CDC criteria for CFS. DNA extracted from blood samples of 186 CFS patients were screened for XMRV provirus and for the closely related murine leukaemia virus by nested PCR using specific oligonucleotide primers. To control for the integrity of the DNA, the cellular beta-globin gene was amplified. Negative controls (water) and a positive control (XMRV infectious molecular clone DNA) were included. While the beta-globin gene was amplified in all 186 samples, neither XMRV nor MLV sequences were detected.

Conclusion: XMRV or MLV sequences were not amplified from DNA originating from CFS patients in the UK. Although we found no evidence that XMRV is associated with CFS in the UK, this may be a result of population differences between North America and Europe regarding the general prevalence of XMRV infection, and might also explain the fact that two US groups found XMRV in prostate cancer tissue, while two European studies did not.

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Competing Interests: The authors have declared that no competing interests exist.

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Introduction

A recent study by Lombardi *et al.* [1] describing a gamma-retrovirus infection in 68 of 101 chronic fatigue syndrome (CFS) patients was notable not only for its claim of a new viral aetiology of a hitherto controversial disease, but also for the fact that proviral DNA could be amplified from the peripheral blood mononuclear cells (PBMC) of 3.75% (8/218) of the healthy controls. This follows an earlier claim that 1.7% (5/300) of healthy Japanese blood donors carried antibodies to the same virus [2]. The virus in question is a recently discovered retrovirus, Xenotropic Murine Leukaemia Virus (MLV)-Related Virus (XMRV).

In the original identification of XMRV in prostate cancer stromal cells, Urisman *et al.* [3] confirmed by sequence analysis that XMRV is not a laboratory contaminant, as is often the case with claims of new retroviral associations with disease. It shares >90% sequence identity in *gag* and *env* (two of the three viral structural genes) with other xenotropic MLVs.

An association between XMRV and prostate cancer was strengthened with the demonstration of XMRV protein expression in malignant epithelial cells [4]. However, these results have not been duplicated in studies conducted in Europe [5–7]. Both prostate cancer and CFS have been linked to an Arg to Gln mutation at codon 462 (R462Q) in the RNaseL gene, an interferon-induced ribonuclease [8]. On activation, RNaseL destroys single stranded cellular and viral RNA, thereby preventing viral replication, blocking protein synthesis, triggering cellular apoptosis and providing an innate anti-viral response. The two US studies are of interest, not only because this would be a further example of a virus association with cancer, but because, they represent the first demonstration of a gamma-retrovirus able to infect human cells, over-riding the intrinsic immune mechanisms that were believed to protect humans from MLV infection.

The XMRV sequences derived from prostate cancer tissue are identical to those from CFS patients, but differ from xenotropic MLV sequences, endorsing a genuine cross-species transmission. However, the claim that XMRV is preferentially found in prostate tumours from patients homozygous for the R462Q variant [3] is not borne out by the second prostate cancer study to find XMRV in patients [4], nor was the genetic variant detected in CFS patients carrying XMRV [5].

The finding of Lombardi *et al.* of a 67% XMRV infection rate among CFS patients, if confirmed, would have a serious impact on understanding the pathogenesis of this complex and debilitating disease and its treatment. Therefore, it was important to determine if CFS sufferers in the UK were carriers of XMRV. We have screened DNA extracts from the blood of CFS sufferers by PCRs targeted at an XMRV-specific sequence and at a sequence conserved amongst most murine retroviruses (MRV).

Methods

Patients

All patients gave written informed consent for the use of their DNA to test aetiological theories of CFS, and the study was approved by the South London and Maudsley NHS Trust Ethics Committee. The study recruited 186 patients (62% female, age range 19–70, mean 39.6±11.3years) from consecutive referrals to the CFS clinic at King's College Hospital, London. All patients had undergone medical screening to exclude detectable organic illness, including a minimum of physical examination, urinalysis, full blood count, urea and electrolytes, thyroid function tests, liver function tests, 9 a.m. cortisol and ESR. Patients were interviewed using a semi-structured interview for CFS [9] to determine whether they met international consensus criteria for CFS. All subjects met the CDC criteria [10]; patients with the Fukuda-specified exclusionary psychiatric disorders, or somatisation disorder (as per DSM-IV), were not included. The patient set studied is a well-characterised and representative sample of CFS patients who have been described previously: all were routine clinic attendees, referred within the UK National Health Service, who had taken part in prior studies of neuroendocrine functioning [11] and/or of cognitive behaviour therapy [12]. As is typical of the patients seen in this tertiary care centre, they were markedly unwell. Few were working, and 19% were members of patient support groups for CFS/ME [12–14]. The levels of fatigue in this sample were high (mean Chalder Fatigue Scale, 26.3±5.4) [15], as were levels of disability (mean Work and Social Adjustment Scale, total score 28.2±7.2) [16]. The mean GHQ-12 score [17] was 19.7±8.1. Patients had been unwell for a median of 4.0 y (range 1–28 y). Of note was that 45% said their illness definitely related to a viral illness and 45% said it might relate to a viral illness. Overall, we conclude that this sample is typical of CFS patients seen in specialist clinical services in the UK. We also know from collaborative studies that our patients resemble those seen in other specialist CFS services in the United States and Australia [18].

PCR detection of XMRV and MLV sequences. DNA was extracted from EDTA whole blood using a standard phenol-based organic deproteinisation procedure [19]. DNA concentrations were determined by absorbance at 260 nm (A_{260}). Each sample was amplified in three nested PCRs using primers targeted to an XMRV-specific sequence, to a sequence conserved amongst most MLV and, as a control for sample addition and PCR-inhibition, to a human beta-globin (hBG) sequence (Table 1). Each first-round reaction was performed in a 25 µl volume containing 0.5 units TaqGold (Applied BioSystems, Warrington, UK), 1 x TaqGold reaction buffer (Applied BioSystems), 1.5 mM Mg^{2+}, 200 mM each dNTP, 2.5 pmol each primer to which 5 µl DNA extract or control was added. Reaction conditions were one cycle of 94°C, 8 minutes, 35 cycles of 94°C 30 seconds, 55°C 30 seconds, 72°C 30 seconds and one cycle of 72°C, 7 minutes. Second round reaction mixes were identical to the first round and the sample was a 1 µl transfer from the first round reactions. Second round reaction conditions were as for the first round over 30 cycles. PCR amplicons were visualised on a 1% agarose gel stained with ethidium bromide. Each PCR run consisted of test samples, six negative (water) and two positive controls. The positive control was a dilution of a plasmid with a full-length XMRV (isolate VP62) insert, generously gifted by Dr R. Silverman. To validate the sensitivity of the PCR, an end-point dilution of the plasmid was performed. To determine specificity of the PCR, a sample of human DNA from the LNCaP prostate cancer cell line (American Type Culture Collection, code CRL-1740) was amplified with the XMRV and MLV primer sets. To ensure integrity of the DNA extracts, three randomly selected samples were titrated to end-point using the hBG PCR to determine if the PCR copy number equated with the A_{260}. To determine if the DNA extracts exhibited low level non-specific inhibition of PCR, 10 samples were subjected to 30 cycles of the first round hBG PCR (reaction mix and conditions as above) followed by 40 cycles of a nested real-time SYBR-green PCR using the SYBR-green Fast PCR kit (Roche, Lewes UK) according to the manufacturer's instructions.

Table 1. Oligonucleotide Primers.

Target	Sequence	Location
XMRV	Forward outer 5'CATTCTGTATCAGTTAACCTAC 3'	411–432[1]
	Reverse outer 5' ATGATCTCGAGAACACTTAAAG 3'	606–588[1]
	Forward inner 5' GACTTTTTGGAGTGGCTTTGT 3'	441–461[1]
	Reverse inner 5' ACAGAAGAACAACAAAACAAATC 3'	566–544[1]
MLV	Forward outer 5' GGATCAAGCCCCACATACAG 3'	2796–2847[1]
	Reverse outer 5' CATCAAACAGGGTGGGACTG 3'	3179–3160[1]
	Forward inner 5' AGAAGTCAACAAGCGGGTGG 3'	2926–2945[1]
	Reverse inner 5' GGTGGAGTCTCAGGCAGAAA 3'	3062–3043[1]
hBG	Forward outer 5' TGGTGGTCTACCCTTGGACC 3'	148–162[2]
	Reverse outer 5' GAGGTTGTCCAGGTGAGCCA 3'	296–277[2]
	Forward inner 5' GAGGTTCTTTGAGTCCTTTGG 3'	170–190[2]
	Reverse inner 5' CATCACTAAAGGCACCGAGCA 3'	273–253[2]

Locations in GenBank accessions [1]EF185282, [2]NM000518.4.
doi:10.1371/journal.pone.0008519.t001

Results

Nested PCR Validation

Based on A_{260} of the purified plasmid, both primer sets (XMRV, MLV) were able to amplify a single target copy added to the reaction. Amplification of 600 ng of LNCaP cellular DNA added to XMRV and MLV PCRs yielded no non-specific bands when viewed on an ethidium bromide-stained agarose gel. Quantification of DNA samples from three randomly selected test samples by end-point dilution PCR with the hBG primer set showed concurrence of the PCR-determined copy number with A_{260}, thus indicating integrity of the DNA preparations. Nested real-time amplification of 10 samples showed no evidence of non-specific inhibition as determined by the slope of the amplification curves and the height of the signal plateau.

PCR Analysis of Test Samples

Input DNA ranged from 10 to 600 ng (1.6×10^3 to 1.1×10^5 cell equivalents) as determined by A_{260} of which 149 samples had an input of >100 ng and 106 samples >200 ng. None of the 186 test samples analysed yielded a specific PCR product with either the XMRV or MLV primer sets and no non-specific PCR products were observed. A specific hBG product was amplified from all 186 test samples. The positive control was amplified in each run by the

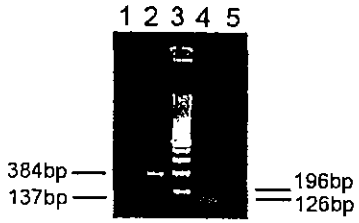

Figure 1. PCR products of the XMRV VP62 clone. Primers are generic to MLV (lanes 1 and 2) or specific to XMRV (lanes 4 and 5). The sizes of the respective fragments are shown. Lane 3–200 bp molecular size ladder.
doi:10.1371/journal.pone.0008519.g001

XMRV and MLV primer sets. A stained gel of the XMRV and MLV PCR products is shown in figure 1 and a representative sample of our results with CFS DNA and MLV primers is shown in figure 2.

Discussion

Unlike the study of Lombardi *et al.*, we have failed to detect XMRV or closely related MRV proviral DNA sequences in any sample from CFS cases. There have been numerous claims for an infective aetiology to CFS over the years, not least because, as in this sample, many patients report that their symptoms were triggered by an infective episode. Prospective epidemiological studies have confirmed that certain infective agents, for example Epstein Barr virus, are unequivocally associated with subsequent CFS [20], even if the mechanisms are unclear and almost certainly multi factorial. Nearly two decades ago, sequences from another retrovirus, the human T-lymphotropic virus type II, were amplified from the PBMCs of 10/12 (83%) adult and 13/18 paediatric CFS patients, but not from healthy control subjects [21]. However, subsequent studies carried out on small numbers (20–30) of CFS patients, failed to confirm evidence for HTLV (type I or II) [22–25] or other retroviruses, including the closely-related simian T lymphotropic virus type I, the prototype foamy virus, simian retrovirus, bovine and feline leukaemia viruses [26] and HIV-1 [23].

The Lombardi paper is the first to study a significantly larger number of people than that in any previous study and to detect a virus only recently discovered. Our study resembles that of Lombardi *et al.* in certain respects. Both studies use the widely accepted 1994 clinical case definition of CFS[10]. Lombardi *et al.* reported that their cases "presented with severe disability" and we provide quantifiable evidence confirming high levels of disability in our subjects. Our subjects were also typical of those seen in secondary and tertiary care in other centres.

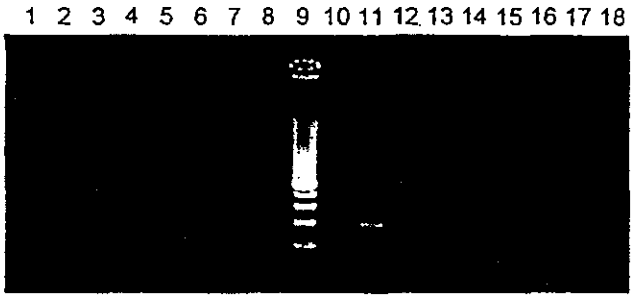

Figure 2. Nested PCR from the DNA of 8 CFS patients. Products of generic MLV primers (including XMRV) are shown. Lanes 1–8, CFS patient DNA (2nd round); lanes 9 and 10, XMRV 2nd round and 1st round positive controls; lanes 11 and 12, DNA of uninfected cell line LNCaP; lanes 13–18, water controls.
doi:10.1371/journal.pone.0008519.g002

Our own study also differs from that of Lombardi in other respects. Firstly, the PCR operator was blinded to the provenance of the DNA samples. In fact, with the exception of the PCR controls, all 186 DNA test samples originated from CFS patients. Care was taken to grow the XMRV plasmid in a laboratory in which no MLV had been cultured and no MLV vectors used and the PCR was carried out in a CPA-accredited Molecular Diagnostics Unit which processes only human tissue. Multiple (six) water (negative) controls were included in every run to detect low level contamination and a PCR to amplify a sequence that is conserved in most murine leukaemia viruses was included in order to expose any circulating MLV contamination and to detect any variant of XMRV that might be circulating in the UK CFS population.

Based on our molecular data, we do not share the conviction that XMRV may be a contributory factor in the pathogenesis of CFS, at least in the U.K.

Acknowledgments

The assistance of Sarah Bull in data collection and processing is gratefully acknowledged.

Author Contributions

Conceived and designed the experiments: SK MM. Performed the experiments: OWE SK. Analyzed the data: SK MM. Contributed reagents/materials/analysis tools: SK GW DC SW AC. Wrote the paper: SK MM. Facilitated the study by setting up the collaboration: JW. Responsible for providing samples and associated data from a well characterised and valuable cohort of subjects: SW.

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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 2010年1月25日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり		研究報告の公表状況	2009-2010 Influenza Season Week 1 ending January 9, 2010 : 3	公表国 米国	
販売名（企業名）	別紙のとおり					

研究報告の概要	使用上の注意記載状況・その他参考事項等
問題点：the Iowa Department of Public Health から、ヒトにおける初のブタインフルエンザA(H3N2)感染事例が報告された。 ヒトにおける新規インフルエンザAウイルスの感染事例1例が the Iowa Department of Public Health から報告された。患者は2009年9月に発症したが、入院の必要は無く、回復した。同ウイルスはブタインフルエンザA（H3N2）と同定され、2009年11月に精査された。ブタからの暴露は不明である一方、同ウイルスのヒトーヒト感染の証拠は認められていない。新規インフルエンザA感染事例の速やかな同定及び精査は流行の拡大規模及びヒトーヒト感染の可能性の評価に重要である。新規インフルエンザAウイルスのヒト感染における調査は通年で実施されている。	記載なし。

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。

MedDRA/J ver.12.0

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人免役グロブリン、⑦乾燥ペプシン処理人免疫グロブリン、⑧乾燥ペプシン処理人免疫グロブリン、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乾燥スルホ化人免疫グロブリン、⑬乾燥スルホ化人免疫グロブリン、⑭乾燥スルホ化人免疫グロブリン*、⑮乾燥濃縮人活性化プロテインC、⑯乾燥濃縮人血液凝固第Ⅷ因子、⑰乾燥濃縮人血液凝固第Ⅷ因子、⑱乾燥濃縮人血液凝固第Ⅷ因子、⑲乾燥濃縮人血液凝固第Ⅷ因子、⑳乾燥濃縮人血液凝固第Ⅸ因子、㉑乾燥濃縮人血液凝固第Ⅸ因子、㉒乾燥濃縮人血液凝固第Ⅸ因子、㉓乾燥濃縮人血液凝固第Ⅸ因子、㉔乾燥抗破傷風人免疫グロブリン、㉕乾燥抗破傷風人免疫グロブリン、㉖抗HBs人免疫グロブリン、㉗抗HBs人免疫グロブリン、㉘トロンビン、㉙フィブリノゲン加第ⅩⅢ因子、㉚フィブリノゲン加第ⅩⅢ因子、㉛乾燥濃縮人アンチトロンビンⅢ、㉜乾燥濃縮人アンチトロンビンⅢ、㉝ヒスタミン加人免疫グロブリン製剤、㉞ヒスタミン加人免疫グロブリン製剤、㉟人血清アルブミン*、㊱人血清アルブミン*、㊲乾燥ペプシン処理人免役グロブリン*、㊳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“化血研”ガンマーグロブリン、⑤ガンマーグロブリン筋注450mg/3mL「化血研」、⑥ガンマーグロブリン筋注1500mg/10mL「化血研」、⑦献血静注グロブリン“化血研”、⑧献血グロブリン注射用2500mg「化血研」、⑨献血ベニロンーⅠ、⑩献血ベニロンーⅠ静注用500mg、⑪献血ベニロンーⅠ静注用1000mg、⑫献血ベニロンーⅠ静注用2500mg、⑬献血ベニロンーⅠ静注用5000mg、⑭ベニロン*、⑮注射用アナクトC2,500単位、⑯コンファクトF、⑰コンファクトF注射用250、⑱コンファクトF注射用500、⑲コンファクトF注射用1000、⑳ノバクトM、㉑ノバクトM注射用250、㉒ノバクトM注射用500、㉓ノバクトM注射用1000、㉔テタノセーラ、㉕テタノセーラ筋注用250単位、㉖ヘパトセーラ、㉗ヘパトセーラ筋注200単位/mL、㉘トロンビン“化血研”、㉙ボルヒール、㉚ボルヒール組織接着用、㉛アンスロビンP、㉜アンスロビンP500注射用、㉝ヒスタグロビン、㉞ヒスタグロビン皮下注用、㉟アルブミン20%化血研*、㊱アルブミン5%化血研*、㊲静注グロブリン*、㊳アンスロビンP1500注射用
報告企業の意見	インフルエンザウイルス粒子は70～120nmの球形または多形性で、8本の分節状マイナス一本鎖RNAを核酸として有する。エンベロープの表面に赤血球凝集素(HA)とノイラミダーゼ(NA)のスパイクを持ち、その抗原性により16種類のHA亜型および9種類のNA亜型に分類される。 今回の報告はヒトにおける初めてのブタインフルエンザA(H3N2)感染事例報告であるが、感染経路は明らかになっていない。また、ヒトに対し高病原性であるような情報も示されていない。 弊所の血漿分画製剤の製造工程には、冷エタノール分画工程、ウイルス除去膜ろ過工程あるいは加熱工程等の原理の異なるウイルス除去及び不活化工程が存在しているので、ウイルスクリアランスが期待される。各製造工程のウイルス除去・不活化効果は、「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)」に従い、ウシウイルス性下痢ウイルス(BVDV)、仮性狂犬病ウイルス(PRV)、ブタパルボウイルス(PPV)、A型肝炎ウイルス(HAV)または脳心筋炎ウイルス(EMCV)をモデルウイルスとして、ウイルスプロセスバリデーションを実施し、評価を行っている。今回報告したインフルエンザウイルスは、エンベロープの有無、核酸の種類等からモデルウイルスとしてはBVDVが該当すると考えられるが、上記バリデーションの結果から、弊所の血漿分画製剤の製造工程がBVDVの除去・不活化効果を有することを確認している。また、これまでに当該製剤によるインフルエンザの報告例は無い。以上の点から、当該製剤はインフルエンザウイルス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

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

2009-2010 Influenza Season
Week 1 ending January 9, 2010

All data are preliminary and may change as more reports are received.

Synopsis: During week 1 (January 3-9, 2010), influenza activity continued to decrease in the U.S.

- 139 (3.6%) specimens tested by U.S. World Health Organization (WHO) and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories and reported to CDC/Influenza Division were positive for influenza.
- All subtyped influenza A viruses reported to CDC were 2009 influenza A (H1N1) viruses.
- One human infection with a novel influenza A virus was reported.
- The proportion of deaths attributed to pneumonia and influenza (P&I) was below the epidemic threshold.
- Seven influenza-associated pediatric deaths were reported. Six deaths were associated with 2009 influenza A (H1N1) virus infection and one was associated with an influenza A virus for which the subtype was undetermined.
- The proportion of outpatient visits for influenza-like illness (ILI) was 1.9% which is below the national baseline of 2.3%. One of the 10 regions (region 9) reported ILI above their region-specific baseline.
- No states reported widespread influenza activity, nine states reported regional influenza activity, the District of Columbia, Puerto Rico, and 15 states reported local influenza activity, Guam and 24 states reported sporadic influenza activity, and the U.S. Virgin Islands and two states reported no influenza activity.

National and Regional Summary of Select Surveillance Components

	Data for current week			Data cumulative since August 30, 2009 (Week 35)*						
HHS Surveillance Regions**	Out-patient ILI†	% positive for flu‡	Number of jurisdictions reporting regional or widespread activity§	A (H1)	A (H3)	2009 A (H1N1)	A (unable to sub-type)¥	A (Subty-ping not perfor-med)	B	Pediatric Deaths
Nation	Normal	3.6%	9 of 54	29	52	61,332	313	19,225	228	236
Region 1	Normal	3.0%	1 of 6	4	2	3,320	14	469	10	6
Region 2	Normal	4.9%	2 of 4	4	4	1,484	0	1,098	9	11
Region 3	Normal	2.8%	1 of 6	3	7	10,554	48	1,456	16	13
Region 4	Normal	6.5%	2 of 8	0	5	7,326	90	4,123	63	45
Region 5	Normal	3.1%	0 of 6	7	23	9,356	52	1,333	15	33
Region 6	Normal	2.2%	1 of 5	0	3	3,475	45	4,722	41	66
Region 7	Normal	3.0%	0 of 4	3	1	3,299	3	769	3	8
Region 8	Normal	3.0%	0 of 6	6	2	9,766	0	3,770	59	13
Region 9	Elevated	4.8%	2 of 5	0	4	8,175	47	1,167	10	31
Region 10	Normal	7.3%	0 of 4	2	1	4,567	14	318	2	10

*Influenza season officially begins each year at week 40. This season data from week 35 will be included to show the trend of influenza activity before the official start of the 2009-10 influenza season.

**HHS regions (Region 1 CT, ME, MA, NH, RI, VT; Region 2: NJ, NY, Puerto Rico, US Virgin Islands; Region 3: DE, DC, MD, PA, VA, WV; Region 4: AL, FL, GA, KY, MS, NC, SC, TN; Region 5: IL, IN, MI, MN, OH, WI; Region 6: AR, LA, NM, OK, TX; Region 7: IA, KS, MO, NE; Region 8: CO, MT, ND, SD, UT, WY; Region 9: AZ, CA, Guam, HI, NV; and Region 10: AK, ID, OR, WA). Use of the national baseline for regional data or regional baselines for state data is not appropriate.

† Elevated means the % of visits for ILI is at or above the national or region-specific baseline.

‡ National data are for current week; regional data are for the most recent three weeks.

§ Includes all 50 states, the District of Columbia, Guam, Puerto Rico, and U.S. Virgin Islands.

¥ Subtyping results for the majority of specimens in this category were inconclusive because of low virus titers.

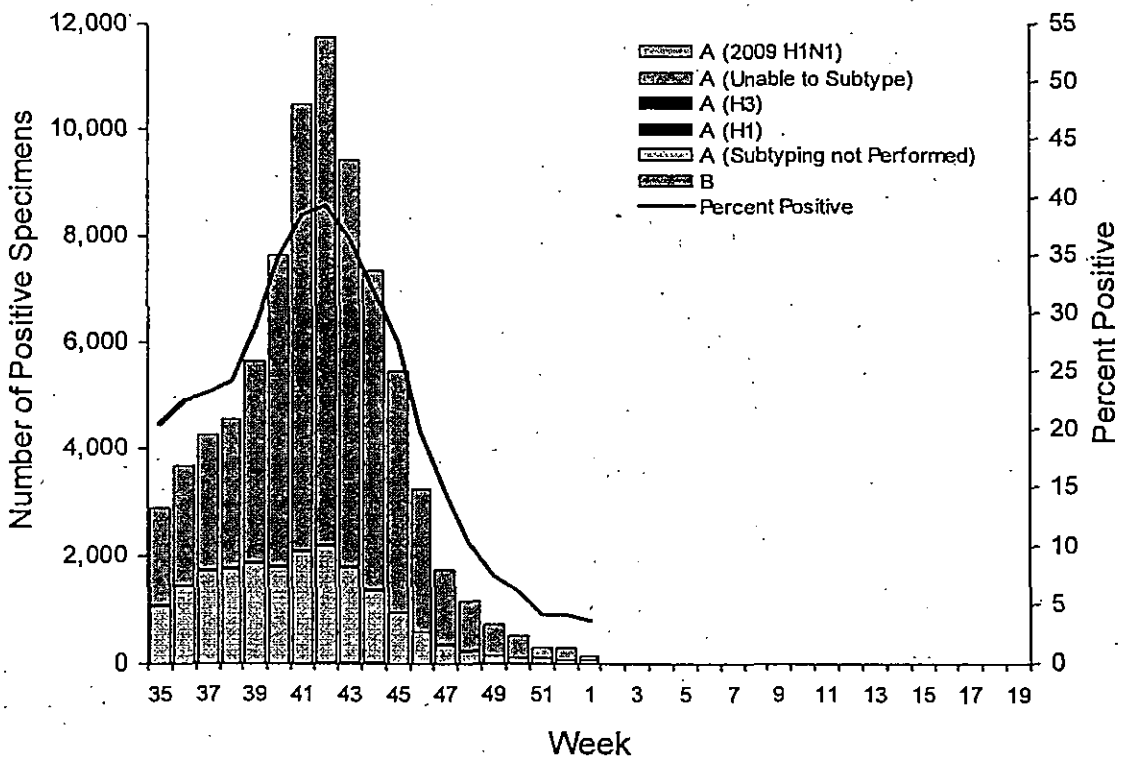
U.S. Virologic Surveillance: WHO and NREVSS collaborating laboratories located in all 50 states and Washington D.C., report to CDC the number of respiratory specimens tested for influenza and the number positive by influenza type and subtype. The results of tests performed during the current week are summarized in the table below.

	Week 1
No. of specimens tested	3,886
No. of positive specimens (%)	139 (3.6%)
Positive specimens by type/subtype	
Influenza A	137 (98.6%)
A (2009 H1N1)	78 (56.9%)
A (subtyping not performed)	58 (42.3%)
A (unable to subtype)*	1 (0.7%)
A (H3)	0 (0.0%)
A (H1)	0 (0.0%)
Influenza B	2 (1.4%)

*Subtyping results for the specimen in this category was inconclusive because of low levels of viral RNA.

During week 1, influenza B viruses co-circulated at low levels with 2009 influenza A (H1N1) viruses. All subtyped influenza A viruses reported to CDC this week were 2009 influenza A (H1N1) viruses.

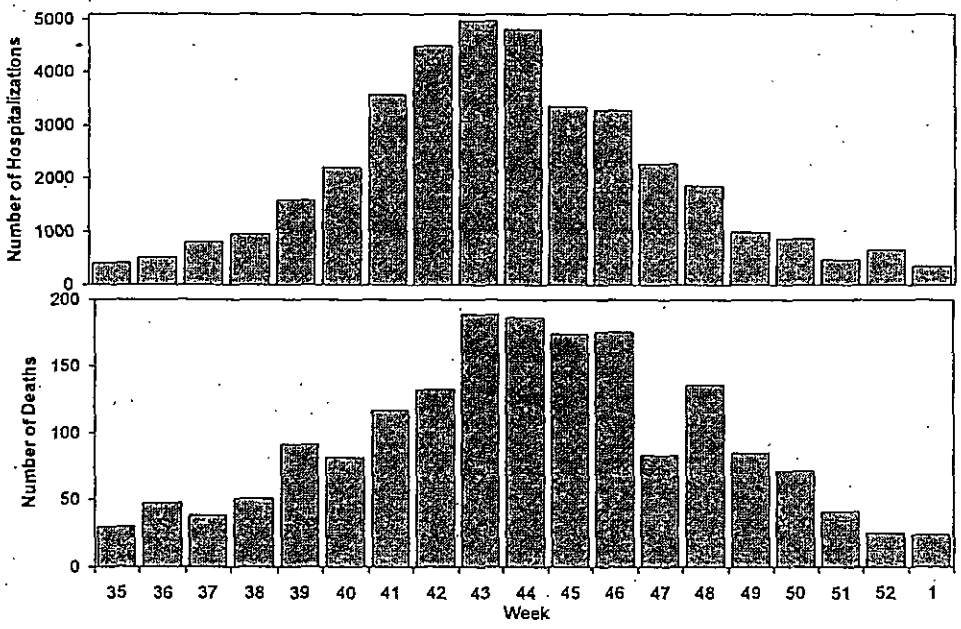
Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, August 30, 2009-January 9, 2010



Novel Influenza A Virus: One case of human infection with a novel influenza A virus was reported by the Iowa Department of Public Health. The case patient had onset of symptoms in September 2009, but did not require hospitalization and has fully recovered. The virus was identified as swine influenza A (H3N2) and investigated in November 2009. No clear exposure to swine was identified, but no evidence of sustained human-to-human transmission with this virus was found. Early identification and investigation of novel influenza A cases is critical to evaluate the extent of the outbreak and possible human-to-human transmission. Surveillance for human infections with novel influenza A viruses is conducted year-round.

Pneumonia and Influenza Hospitalization and Death Tracking: The Aggregate Hospitalization and Death Reporting Activity (AHDRA) system was implemented on August 30, 2009, and replaces the weekly report of laboratory confirmed 2009 H1N1-related hospitalizations and deaths that began in April 2009. Jurisdictions can now report to CDC counts of hospitalizations and deaths resulting from all types or subtypes of influenza, not just those from 2009 H1N1 influenza virus. To allow jurisdictions to implement the new case definition, counts were reset to zero on August 30, 2009. From August 30, 2009 – January 9, 2010, 38,454 laboratory-confirmed influenza-associated hospitalizations and 1,779 laboratory-confirmed influenza-associated deaths were reported to CDC. CDC will continue to use its traditional surveillance systems to track the progress of the 2009-10 influenza season.

Weekly Laboratory-Confirmed Influenza-Associated Hospitalizations and Deaths Reported to AHDRA, National Summary, August 30, 2009 – January 9, 2010



Antigenic Characterization: CDC has antigenically characterized one seasonal influenza A (H1N1), seven influenza A (H3N2), six influenza B, and 944 2009 influenza A (H1N1) viruses collected since September 1, 2009.

One seasonal influenza A (H1N1) virus was tested and is related to the influenza A (H1N1) component of the 2009-10 Northern Hemisphere influenza vaccine (A/Brisbane/59/2007).

The seven influenza A (H3N2) viruses tested showed reduced titers with antisera produced against A/Brisbane/10/2007, the 2009-2010 Northern Hemisphere influenza A (H3N2) vaccine component, and were antigenically related to A/Perth/16/2009, the WHO recommended influenza A (H3N2) component of the 2010 Southern Hemisphere vaccine formulation.

Influenza B viruses currently circulating globally can be divided into two distinct lineages represented by the B/Yamagata/16/88 and B/Victoria/02/87 viruses. The influenza B component of the 2009-10 vaccine belongs to the B/Victoria lineage. The six influenza B viruses tested belong to the B/Victoria lineage and are related to the influenza vaccine component for the 2009-10 Northern Hemisphere influenza vaccine (B/Brisbane/60/2008).

Nine hundred forty-two (99.8%) of 944 2009 influenza A (H1N1) viruses tested are related to the A/California/07/2009 (H1N1) reference virus selected by WHO as the 2009 H1N1 vaccine virus. Two viruses (0.3%) tested showed reduced titers with antiserum produced against A/California/07/2009.

Annual influenza vaccination is expected to provide the best protection against those virus strains that are related to the vaccine strains, but limited to no protection may be expected when the vaccine and circulating virus strains are so different as to be from different lineages. Antigenic characterization of 2009 influenza A (H1N1) viruses indicates that these viruses are only distantly related antigenically and genetically to seasonal influenza A (H1N1) viruses, suggesting that little to no protection would be expected from vaccination with seasonal influenza vaccine. It is too early in the influenza season to determine if seasonal influenza viruses will circulate widely or how well the seasonal vaccine and circulating strains will match.

Antiviral Resistance: Since September 1, 2009, one seasonal influenza A (H1N1), eight influenza A (H3N2), one influenza B, and 830 2009 influenza A (H1N1) virus isolates have been tested for resistance to the neuraminidase inhibitors (oseltamivir and zanamivir), and 2,096 2009 influenza A (H1N1) original clinical samples were tested for a single known mutation in the virus that confers oseltamivir resistance. In addition, one seasonal influenza A (H1N1), 11 influenza A (H3N2), and 837 2009 influenza A (H1N1) virus isolates have been tested for resistance to the adamantanes (amantadine and rimantadine). The results of antiviral resistance testing performed on these viruses are summarized in the table below. Additional laboratories perform antiviral testing and report their results to CDC and positive results from that testing are included in the footnote.

Antiviral Resistance Testing Results on Samples Collected Since September 1, 2009.

	Viruses tested (n)	Resistant Viruses, Number (%) Oseltamivir	Viruses tested (n)	Resistant Viruses, Number (%) Zanamivir	Isolates tested (n)	Resistant Viruses, Number (%) Adamantanes
Seasonal Influenza A (H1N1)	1	1 (100.0)	0	0 (0)	1	0 (0)
Influenza A (H3N2)	8	0 (0)	0	0 (0)	11	9 (81.8)
Influenza B	1	0 (0)	0	0 (0)	N/A*	N/A*
2009 Influenza A (H1N1)	2,926	39†‡ (1.3)	830	0 (0)	837	834 (99.6)

*The adamantanes (amantadine and rimantadine) are not effective against influenza B viruses.
†Two screening tools were used to determine oseltamivir resistance: sequence analysis of viral genes and a neuraminidase inhibition assay.
‡ Additional laboratories perform antiviral resistance testing and report their results to CDC. Three additional oseltamivir resistant 2009 influenza A (H1N1) virus has been identified by these laboratories since September 1, 2009, bringing the total number to 42.

All of the subtyped influenza A viruses reported during week 1 were 2009 influenza A (H1N1) viruses, and nearly all of 2009 H1N1 viruses tested since April 2009 have been resistant to the adamantanes (amantadine and rimantadine).

Antiviral treatment with oseltamivir or zanamivir is recommended for all patients with confirmed or suspected influenza virus infection who are hospitalized, are at higher risk for influenza complications, or who have lower respiratory tract or progressive disease. Additional information on antiviral recommendations for treatment and chemoprophylaxis of influenza virus infection is available at http://www.cdc.gov/H1N1flu/recommendations.htm.

2009 influenza A (H1N1) viruses were tested for oseltamivir resistance by a neuraminidase inhibition assay and/or detection of genetic sequence mutation, depending on the type of specimen tested. Original clinical samples were examined for a single known mutation in the virus that confers oseltamivir resistance in currently circulating seasonal influenza A (H1N1) viruses, while influenza virus isolates were tested using a neuraminidase inhibition assay that determines the presence or absence of neuraminidase inhibitor resistance, followed by neuraminidase gene sequence analysis of resistant viruses.

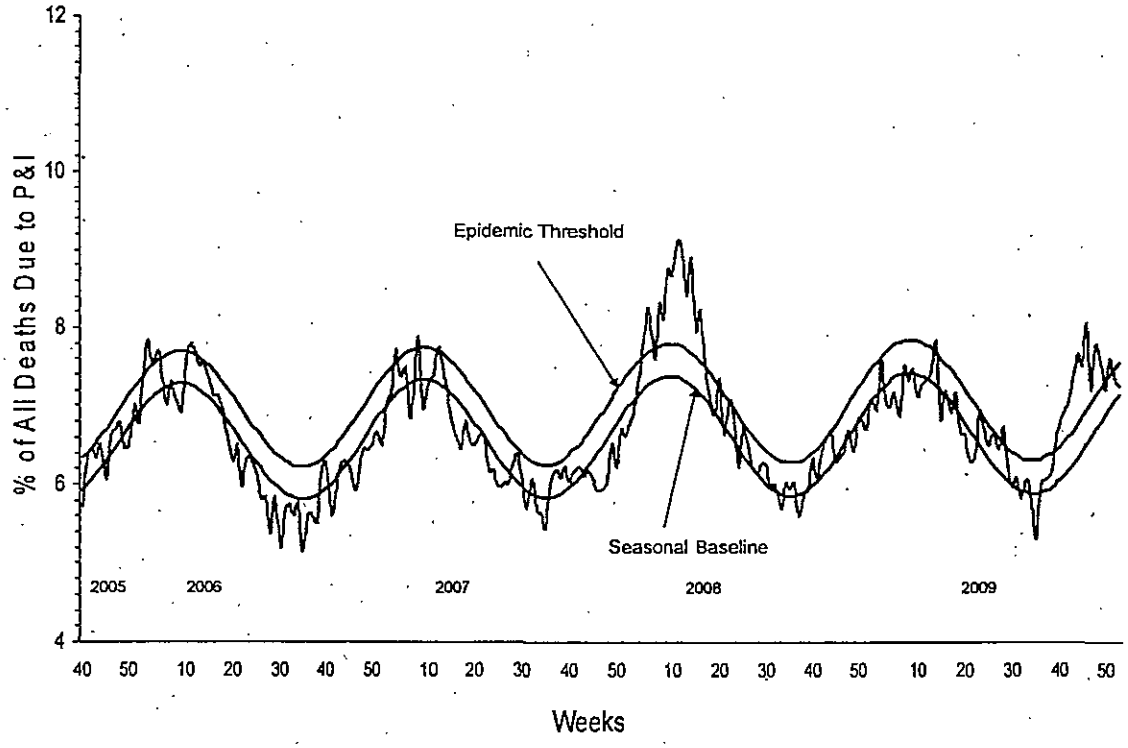
The majority of 2009 influenza A (H1N1) viruses are susceptible to the neuraminidase inhibitor antiviral medication oseltamivir; however, rare sporadic cases of oseltamivir resistant 2009 influenza A (H1N1) viruses have been detected worldwide. A total of 52 cases of oseltamivir resistant 2009 influenza A (H1N1) viruses have been identified in the United States since April 2009. While the total number of cases has not increased over the previous week, one previously reported case was reclassified and one new case was identified. Forty-two of these specimens

were collected after September 1, 2009. The proportion of oseltamivir-resistant 2009 H1N1 viruses does not represent the prevalence of oseltamivir-resistant 2009 H1N1 in the U.S. Most cases were tested because drug resistance was suspected. All tested viruses retain their sensitivity to the neuraminidase inhibitor zanamivir. Of the 52 total cases identified since April 2009, 40 patients had documented exposure to oseltamivir through either treatment or chemoprophylaxis, nine patients are under investigation to determine exposure to oseltamivir, and three patients had no documented oseltamivir exposure. Occasional development of oseltamivir resistance during treatment or prophylaxis is not unexpected. Enhanced surveillance, an increased availability of testing performed at CDC, and an increasing number of public health and other clinical laboratories performing antiviral resistance testing increase the number of cases of oseltamivir resistant 2009 influenza A (H1N1) viruses detected. All cases are investigated to assess the spread of resistant strains in the community.

To prevent the spread of antiviral resistant virus strains, CDC reminds clinicians and the public of the need to continue hand and cough hygiene measures for the duration of any symptoms of influenza, even while taking antiviral medications (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5832a3.htm).

Pneumonia and Influenza (P&I) Mortality Surveillance: During week 1, 7.3% of all deaths reported through the 122-Cities Mortality Reporting System were due to P&I. This percentage was below the epidemic threshold of 7.6% for week 1.

Pneumonia and Influenza Mortality for 122 U.S. Cities
Week ending 1/9/2010



Influenza-Associated Pediatric Mortality: Seven influenza-associated pediatric deaths were reported to CDC during week 1 (Illinois, Michigan, New York [2], Oregon, and Texas [2]). Six deaths were associated with 2009 influenza A (H1N1) virus infection and one was associated with an influenza A virus for which the subtype was undetermined.. The deaths reported during week 1 occurred between October 11 and December 19, 2009.

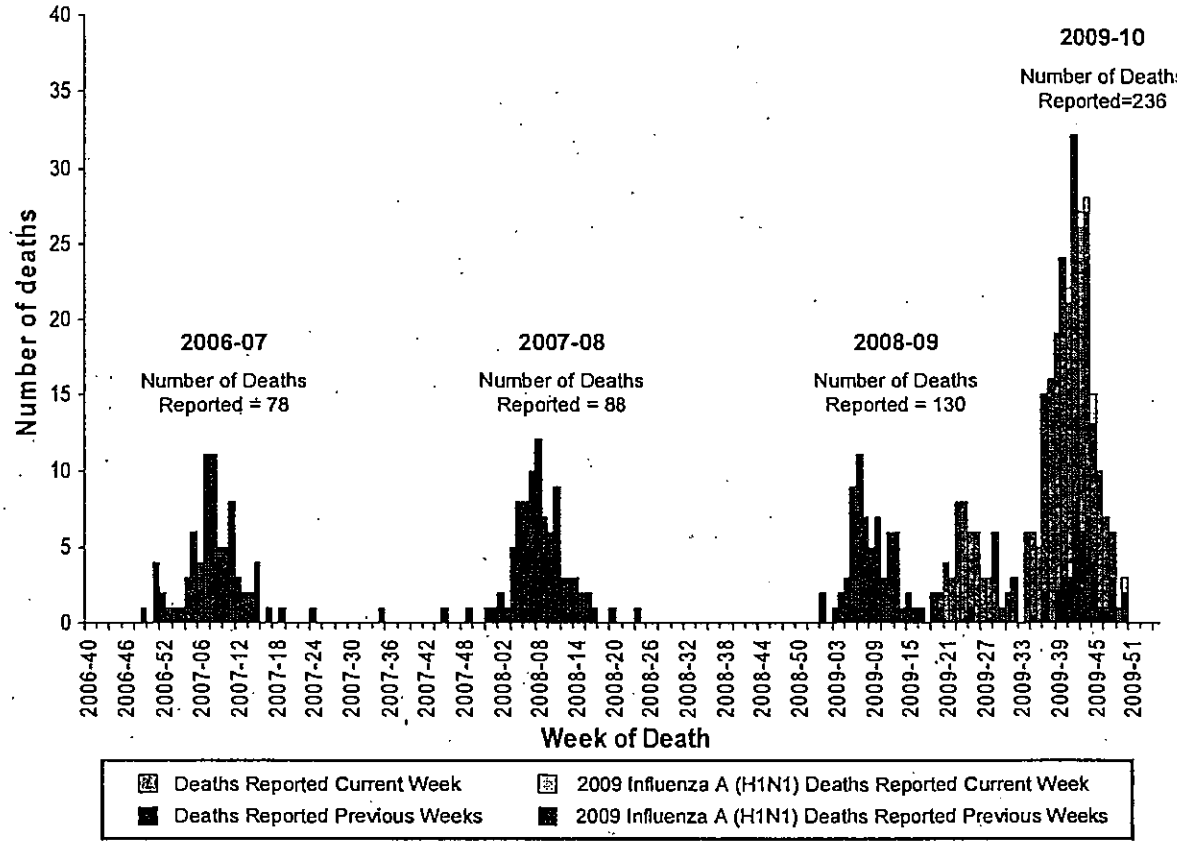
Since August 30, 2009, CDC has received 236 reports of influenza-associated pediatric deaths that occurred during the current influenza season (43 deaths in children less than 2 years old, 26 deaths in children 2-4 years old, 87 deaths in children 5-11 years old, and 80 deaths in children 12-17 years old). One hundred ninety-five (83%) of the 236 deaths were due to 2009 influenza A (H1N1) virus infections, 40 were associated with an influenza A virus for which the subtype is undetermined, and one was associated with an influenza B virus infection. A total of 255 deaths in children associated with 2009 influenza A (H1N1) virus infection have been reported to CDC.

Among the 236 deaths in children, 121 children had specimens collected for bacterial culture from normally sterile sites and 39 (32.2%) of the 121 were positive; *Streptococcus pneumoniae* was identified in 10 (25.6%) of the 39 children and *Staphylococcus aureus* was identified in 11 (28.2%) of the 39 children. Two *S. aureus* isolates were sensitive to methicillin, eight were methicillin resistant, and one did not have sensitivity testing performed. Twenty-six (66.7%) of the 39 children with bacterial coinfections were five years of age or older, and 14 (35.9%) of the 39 children were 12 years of age or older.

Laboratory-Confirmed Influenza-Associated Pediatric Deaths by Date and Type/Subtype of Influenza.

Date	2009 H1N1 Influenza	Influenza A-Subtype Unknown	Seasonal Influenza	Total
Number of Deaths REPORTED for Current Week – Week 1 (Week ending January 9, 2010)	6	1	0	7
Number of Deaths OCCURRED since August 30, 2009	195	40	1	236
Number of Deaths OCCURRED since April 26, 2009	255	43	2	300

Number of Influenza-Associated Pediatric Deaths by Week of Death: 2006-07 season to present

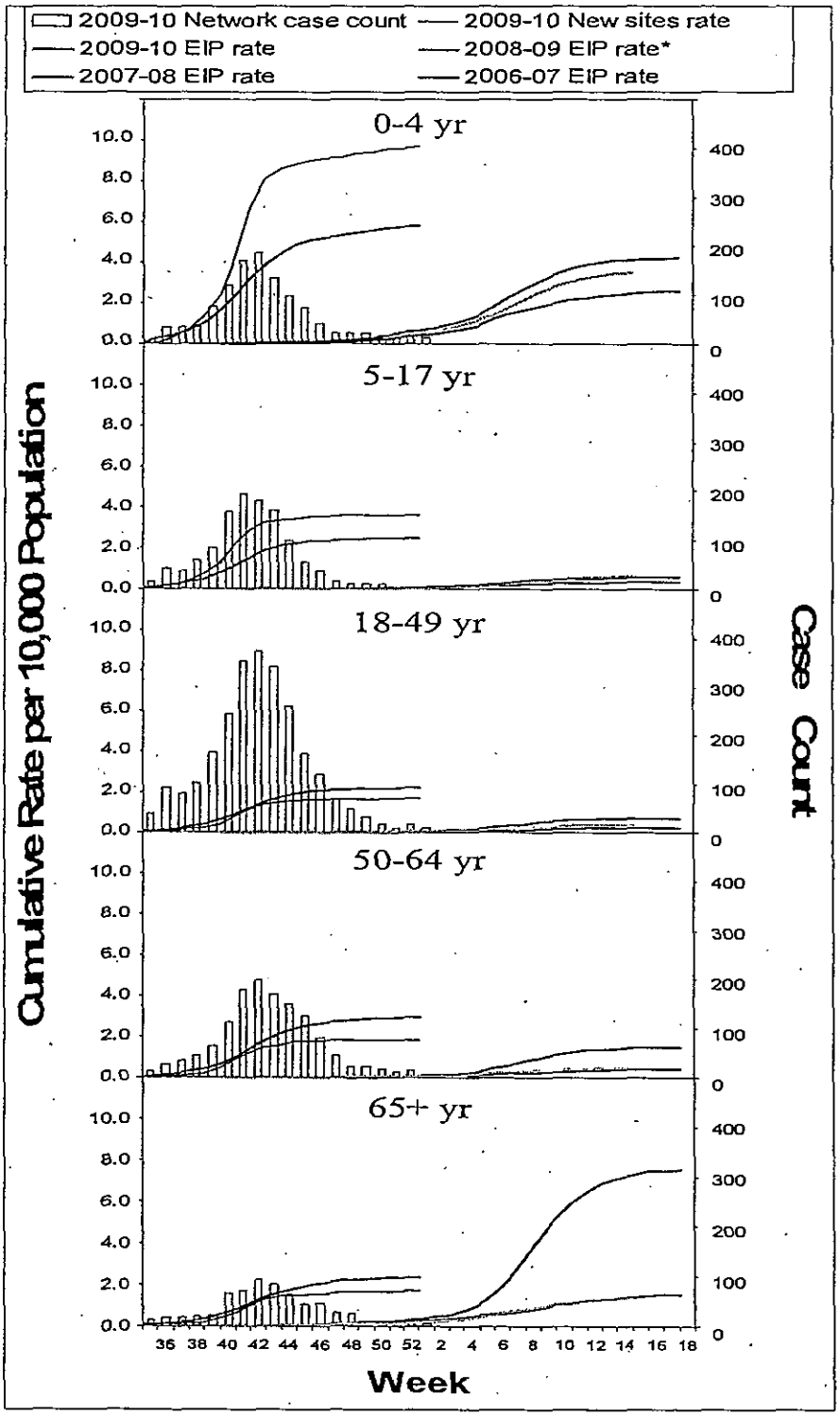


Influenza-Associated Hospitalizations: Laboratory-confirmed influenza-associated hospitalizations are monitored using a population-based surveillance network that includes the 10 Emerging Infections Program (EIP) sites (CA, CO, CT, GA, MD, MN, NM, NY, OR and TN) and 6 new sites (IA, ID, MI, ND, OK and SD).

During September 1, 2009 – January 9, 2010, the following preliminary laboratory-confirmed overall influenza associated hospitalization rates were reported by EIP and the new sites *(rates include influenza A, influenza B, and 2009 influenza A (H1N1)):*

Rates [EIP (new sites)] for children aged 0-4 years and 5-17 years were 5.9 (9.7) and 2.5 (3.6) per 10,000, respectively. Rates [EIP (new sites)] for adults aged 18-49 years, 50-64 years, and ≥ 65 years were 2.2 (1.7), 2.9 (1.8) and 2.4 (1.7) per 10,000, respectively.

EIP Influenza Laboratory-Confirmed Cumulative Hospitalization Rates, 2009-10 and Previous Three Seasons*

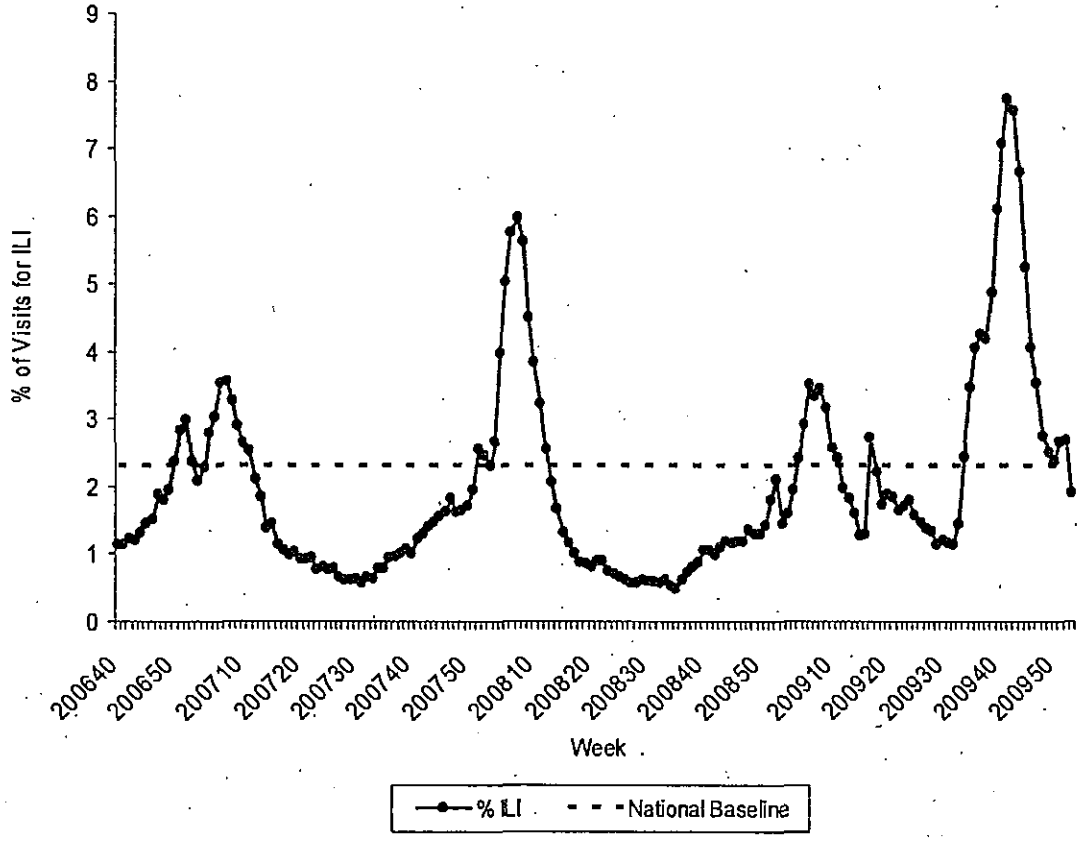


* The 2008-09 EIP rate ended as of April 14, 2009 due to the onset of the 2009 H1N1 season.

Outpatient Illness Surveillance: Nationwide during week 1, 1.9% of patient visits reported through the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) were due to influenza-like illness (ILI). This percentage is below the national baseline of 2.3%.

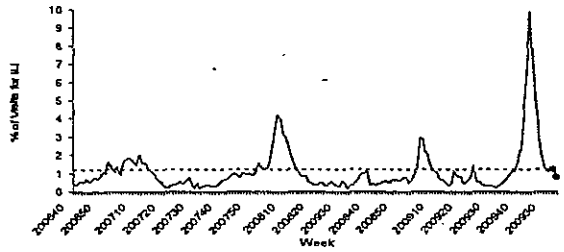
The increase in the percentage of outpatient visits for ILI during weeks 51 and 52 is likely influenced by a reduction in routine health care visits during the holiday season, as has occurred during previous seasons.

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, October 1, 2006 – January 9, 2010

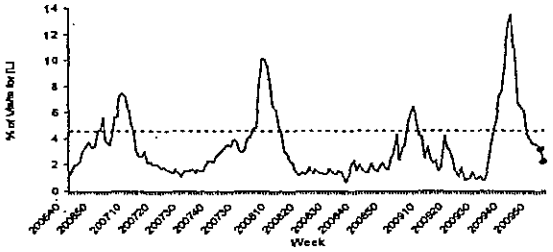


On a regional level, the percentage of outpatient visits for ILI ranged from 0.6% to 3.8% during week 1. One of the 10 regions (Region 9) reported a proportion of outpatient visits for ILI above its region-specific baseline levels. Regions 1, 2, 3, 4, 5, 6, 7, 8, and 10 reported ILI below their region-specific baselines. (Note: Use of the national baseline for regional ILI data or regional baselines for state-level data is not appropriate.)

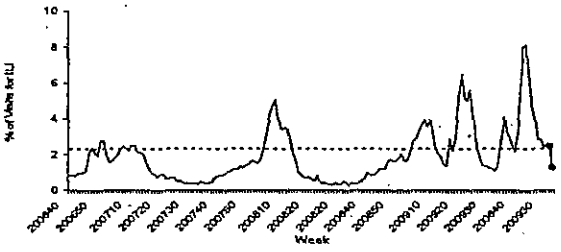
Region 1 - CT, ME, MA, NH, RI, VT



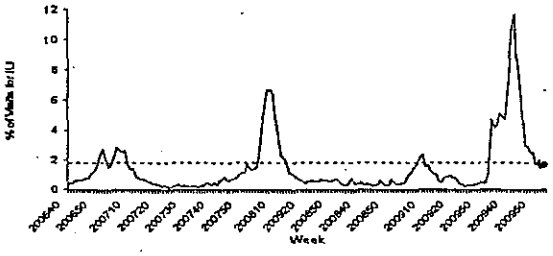
Region 6 - AR, LA, NM, OK, TX



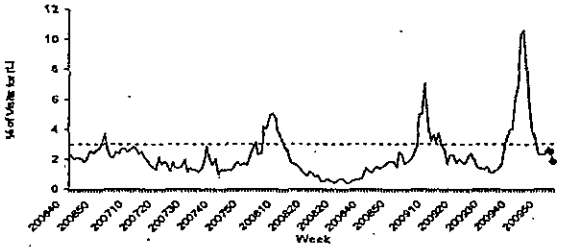
Region 2 - NJ, NY, USVI



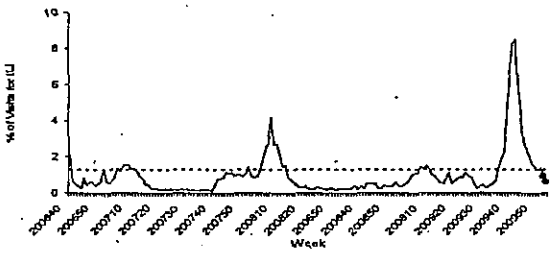
Region 7 - IA, KS, MO, NE



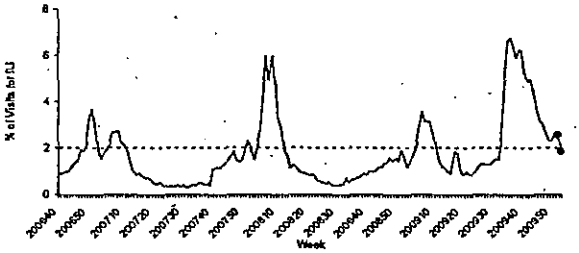
Region 3 - DE, DC, MD, PA, VA, WV



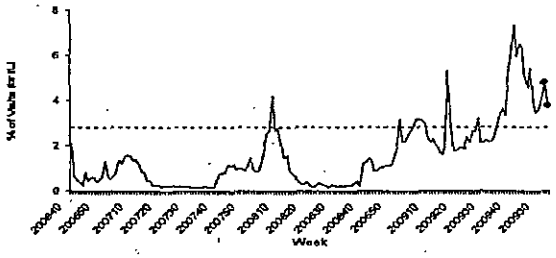
Region 8 - CO, MT, ND, SD, UT, WY



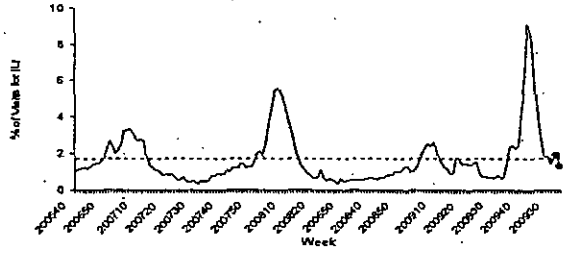
Region 4 - AL, FL, GA, KY, MS, NC, SC, TN



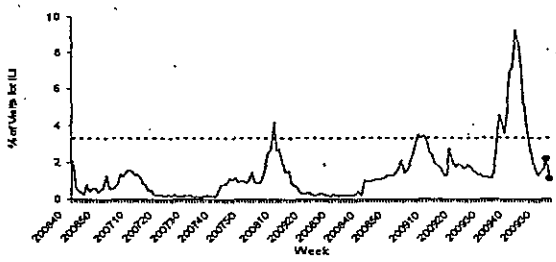
Region 9 - AZ, CA, HI, NV

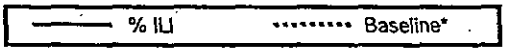


Region 5 - IL, IN, MI, MN, OH, WI



Region 10 - AK, ID, OR, WA





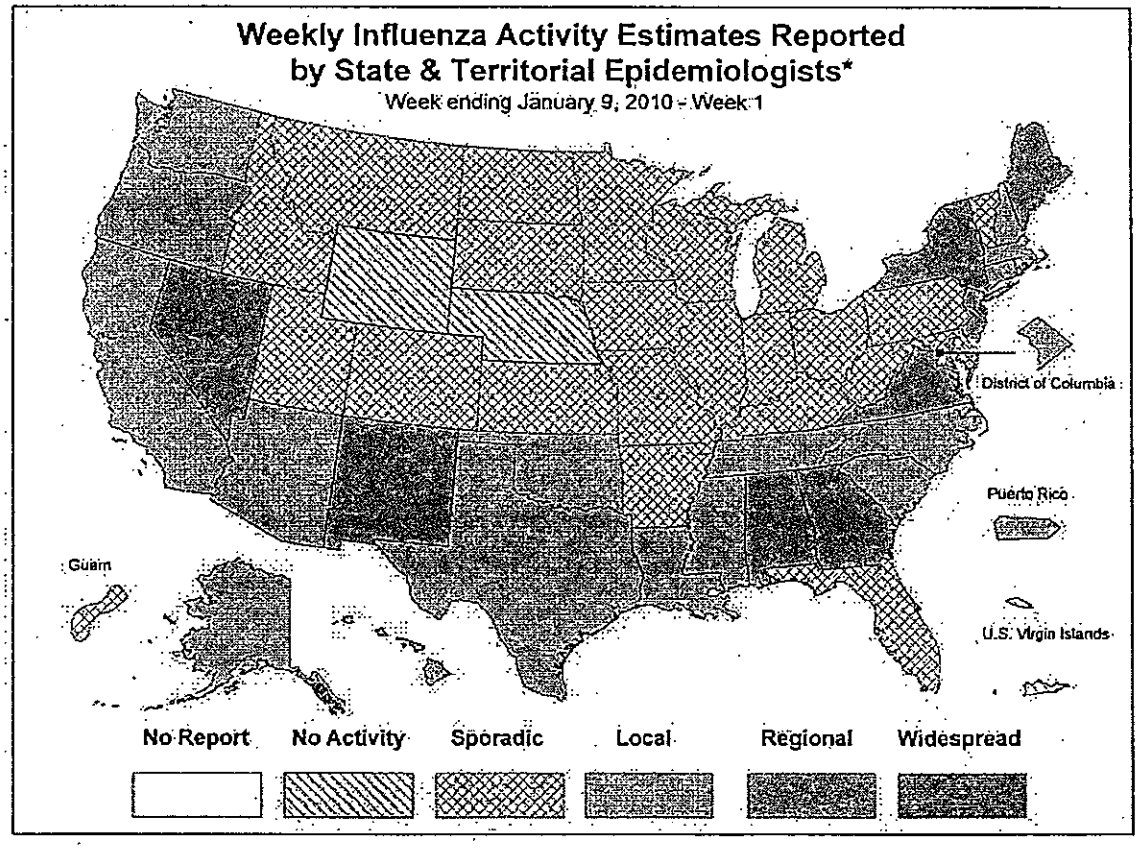
NOTE: Scales differ between regions

*Use of the regional baselines for state data is not appropriate.

Geographic Spread of Influenza as Assessed by State and Territorial Epidemiologists: The influenza activity reported by state and territorial epidemiologists indicates geographic spread of both seasonal influenza and 2009 influenza A (H1N1) viruses and does not measure the severity of influenza activity.

During week 1, the following influenza activity was reported:

- No states reported widespread influenza activity.
- Regional influenza activity was reported by nine states (Alabama, Georgia, Hawaii, Maine, Nevada, New Jersey, New Mexico, New York, and Virginia).
- Local influenza activity was reported by the District of Columbia, Puerto Rico, and 15 states (Alaska, Arizona, California, Connecticut, Louisiana, Massachusetts, Mississippi, New Hampshire, North Carolina, Oklahoma, Oregon, South Carolina, Tennessee, Texas, and Washington).
- Sporadic influenza activity was reported by Guam and 24 states (Arkansas, Colorado, Delaware, Florida, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Michigan, Minnesota, Missouri, Montana, North Dakota, Ohio, Pennsylvania, Rhode Island, South Dakota, Utah, Vermont, West Virginia, and Wisconsin).
- The U.S. Virgin Islands and two states (Nebraska and Wyoming) reported no influenza activity.



* This map indicates geographic spread & does not measure the severity of influenza activity

A description of surveillance methods is available at: http://www.cdc.gov/flu/weekly/fluactivity.htm
Report prepared: January 15, 2010.

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
				2009. 11. 12	該当なし	

一般的名称	人血清アルブミン	研究報告の公表状況		公表国
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)		ABC Newsletter #38. 2009 Oct 23; 13-14.	ヨーロッパ

研究報告の概要

○EU規制当局はインフルエンザパンデミック時の献血条件緩和を検討

欧州連合の血液規制委員会(Blood Regulatory Committee)は、H1N1インフルエンザ・パンデミック時の供給確保のため2つの緩和策を検討していると報告した。ヨーロッパ各国の代表は、パンデミックが深刻化した場合、輸血用血液が10-15%不足するのではと懸念している。血液規制委員会は、ヨーロッパ血液連盟(EBA)や各国の監督官庁に9月末開催の会議への出席を依頼し、血液の安定供給のためにどの基準を緩和するかを検討した。

この結果、インフルエンザ様症状回復後の献血延期期間はEU指令では14日間だが、これを7日間に短縮することがドナー確保に大きな効果があると多くの国が評価した。また、ヘモグロビン値を女性12.5g/dL、男性13.5g/dLから女性12g/dL、男性13g/dLにすることについて合意した。

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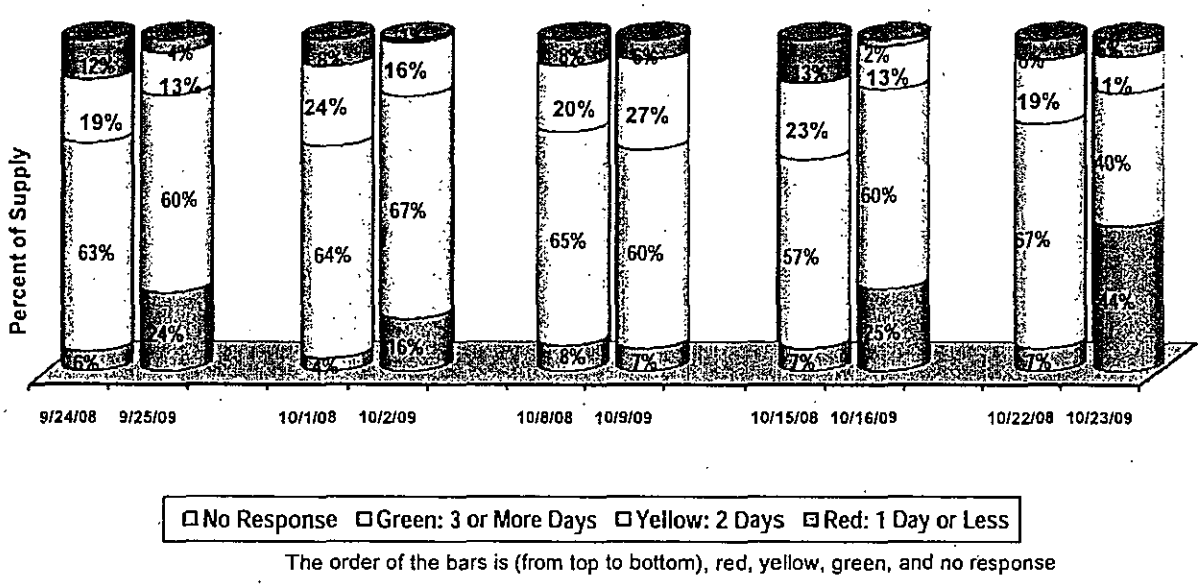
使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
欧州連合の血液規制委員会は、H1N1インフルエンザ・パンデミック時の供給確保のため、インフルエンザ様症状回復後の献血延期期間の短縮とヘモグロビン値の基準の緩和を検討しているとの報告である。 インフルエンザは毎年流行をみる最もポピュラーな疾患であるが、本剤によるいかなるインフルエンザウイルス感染の報告はない。本剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれているため、本剤の安全性は確保されていると考える。	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。更に、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血漿の使用を禁止している。新型インフルエンザが流行した場合、献血者減少につながることも予想されることから、今後も引き続き情報の収集に努める。

STOPLIGHT: Status of the ABC Blood Supply, 2008 vs. 2009



The order of the bars is (from top to bottom), red, yellow, green, and no response

EU Regulator Considers Relaxing Blood Donor Requirements for Flu Pandemic

The Blood Regulatory Committee of DG SANCO, the European regulator for blood requirements, is considering relaxing two of its rules to help assure sufficient blood supplies should an H1N1 flu pandemic create shortages, according to a summary report issued by the committee. Representatives from various European countries and member states are concerned that a severe pandemic could result in a shortage of blood components of up to 10 or 15 percent.

To address this possibility, the committee asked the European Blood Alliance (EBA), the association of national suppliers and regional alliances in Europe, and the national regulators (the so-called "competent authorities" for each European Union [EU] member state or country) to attend a meeting at the end of September to discuss the potential impact of the flu on supply, to consider which rules might be relaxed to maintain an adequate supply, and to gather information from the member states on the measures and contingency plans they are considering in case the blood supply is at risk because an NHIN1 influenza pandemic affects both donors and the staffs of national blood services.

The Blood Regulatory Committee sets standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components. In advance of the meeting, it prepared a working paper providing background information on the following points to be addressed. The paper included:

1. An overview of the potential impact of a pandemic on the blood supply in the EU;
2. Identification of the best ways to correct a potential impact and maintain supply; and
3. An analysis of the potential conflicts between these strategies and the minimum standards for blood and blood components set by the European legislation.

During the meeting, participants were provided with several supporting documents, originating from either member states or the EBA.

(continued on page 14)

EBA Standards (continued from page 13)

Two EU standards were identified as being levers to increase the blood supply on an exceptional and temporary basis in case of a severe shortage. The first involves the deferral period after a potential donor's recovery from a flu-like illness. The EU directive requires that 14 days must elapse between the end of flu-like symptoms in a prospective donor and the donation. Most member states said that reducing this deferral to seven days would have a major effect on accepting donors during a pandemic.

The member states and the committee agreed to request a risk assessment from the European Centre for Disease Control and Prevention on the impact of reducing this deferral period from 14 days to seven or even five days.

In terms of acceptable hemoglobin levels in donors prior to donation, current EU rules state thresholds of 12.5 grams per deciliter (g/dL) for women and 13.5 g/dL for men. There was a consensus among the delegates to the meeting that for a pandemic, these levels could be reduced to 12 and 13 g/dL, respectively, without putting the health of the donors at risk.

FDA prefers to defer decisions. When a similar meeting was held earlier this year with officials from the FDA Centers for Biologics Research and Review and representations of various blood organizations, FDA said it preferred not to address "theoretical" questions on donor criteria. It said it would consider such issues as needed. (Source: Blood Regulatory Committee, Summary Report, 9/29/09) ♦

PEOPLE

Elizabeth G. Nabel will be leaving her current position as director of the National Heart Lung and Blood Institute (NHLBI) at the National Institutes of Health to become the next president of Brigham and Women's Hospital and Faulkner Hospital in Boston, the two medical centers announced on Thursday. She will start the new job on January 1, 2010, when the hospitals' current president, **Gary Gottlieb**, becomes president and chief executive of Boston's Partners HealthCare, the parent organization of the two medical centers and Massachusetts General Hospital. He is replacing **James Mongan**, who will be retiring at the end of the year. Nabel, a cardiologist who graduated from Cornell University Medical College, has served at Brigham and Women's before: she completed her internship and residency in internal medicine there, as well as a clinical and research fellowship in cardiovascular medicine. She served on the faculty at the University of Michigan in the 1990s, and she joined NHLBI in 1999.

CORRECTION: An article in the Oct. 16, 2009, *ABC Newsletter* misstated the relationship between Tom and Sue Zuck. She is his wife. We apologize for the mistake. ♦

Save the Date: FDA Workshop on Emerging Arboviruses

The blood banking community has learned that the Food and Drug Administration will be holding a workshop on emerging arboviruses and recipient safety on Dec. 14-15, 2009 at the National Institutes of Health in Bethesda, Md. The official announcement will be made in the next few weeks. Pre-registration for this free workshop will be required, and forms will be available at the time of the announcement.