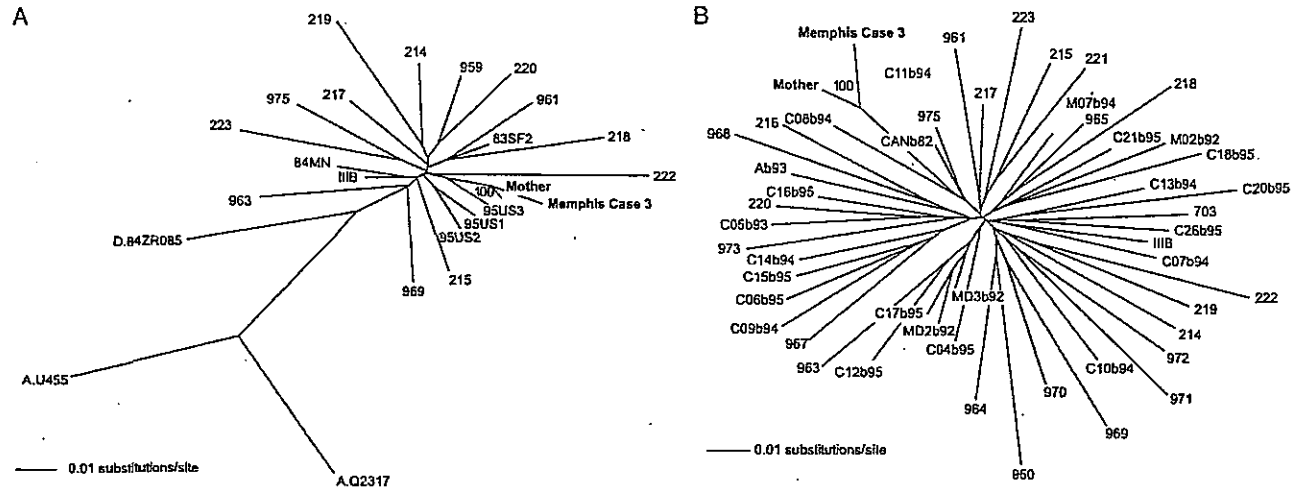

FIGURE 3

Case 3 (Memphis). A, Phylogenetic relationship of the HIV sequences derived from the mother-infant pair of case 3 and unrelated subtype strains from the United States (19 subtype B, 2 subtype A, and 1 subtype D). Shown is a neighbor-joining tree of the gp17 region of *gag*; US subtype B sequences and 1 subtype D sequence were used as reference strains in the tree, and 2 subtype A sequences were used as an outgroup. Only bootstrap values of >70% are indicated for the subtype B branching order. This phylogenetic analysis shows strong clustering, with a 100% bootstrap support for the epidemiological relatedness of the virus from case 3 (Memphis) and the child's mother. B, Phylogenetic relationship of the HIV sequences derived from the mother-infant pair of case 3 from Memphis and 49 unrelated subtype B strains from the United States. Shown is a neighbor-joining tree of the gp41 region of *env*; only bootstrap values of >70% are indicated. US subtype B sequences were used as reference strains in this unrooted tree. Phylogenetic analysis shows strong clustering with a 100% bootstrap support for the relatedness between the virus from case 3 (Memphis) and the child's mother.

ported the epidemiologic conclusion that the mother was the source of HIV-1 infection in the child (Fig 3).

In all 3 cases, additional follow-up interviews with caregivers and physical examinations of the children did not reveal other modes of potential HIV transmission (eg, percutaneous injuries, transfusion or receipt of transplanted tissues, other parenteral exposures or other high-risk contacts [including sexual abuse] with persons infected with HIV in the household).

DISCUSSION

The cases described suggest that HIV may be transmitted through consumption of food that has been premasticated by a person infected with HIV. To our knowledge, this route of HIV transmission has not been reported previously. Bleeding in the oral cavity of the adult infected with HIV, who prechewed the food as documented in cases 1 and 3, was likely the primary source of HIV. The caregivers' lack of access to or lack of adherence to perinatal HIV prophylaxis or antiretroviral therapy probably decreased the suppression of their HIV-1 viral loads. This factor in addition to the children's compromised oral mucosa because of teething or intercurrent oral illness such as candidiasis (reported in case 1) likely facilitated HIV transmission. In addition, tonsillar epithelial factors[13] may have facilitated HIV infection because the tonsils come into contact with blood-tinged food and saliva.

In reviewing the cases, it is important to understand why the first 2 cases were not reported earlier. In cases 1 and 2, the clinicians first contacted the local health department soon after each child's HIV diagnosis. The local and state health departments collaborated with the CDC to conduct an epidemiological investigation. These 2 cases were not reported immediately to the general public for several reasons. Only one of the two possible transmission events was supported by phylogenetic data. Prechewing as a mode of HIV transmission had not been described, and ample data at the time indicated that routine household contact and kissing were not associated with a significantly increased risk of oral HIV transmission. In case 1, transmission through child sexual abuse, a known mode of pediatric HIV transmission that is difficult to establish, and needle-stick exposures were denied but could not be absolutely ruled out. The report of a third possible case, supported by laboratory data, provided the impetus for this report.

Although the practice of premasticating food for children has been described in various parts of the world,[3–8,14–16] including the United States, the extent of this practice is not well known. In the late 1980s, a first-year medical student's observation of this practice prompted a survey of black patients at a primary care pediatrics clinic at the University of Nebraska Medical Center.[7] Although the reports of several infant-feeding surveys conducted at about this time did not mention the practice of premastication, 45 (65%) of 68 adult caregivers in the Nebraska survey acknowledged prechewing food for their infants, and 90% reported knowledge

of this practice.[7] More recently, a study of oral health in a random sample of Alaska Native children (aged 12–36 months) and their caregivers documented that 86.2% of caregivers were currently prechewing or had prechewed food for their infants.[8]

From October 2005 to May 2007, the US Food and Drug Administration, in conjunction with the CDC and other federal agencies, conducted the Infant Feeding Practices Study II,[17] which collected data from responses to questionnaires mailed to a sample of US women who had given birth to term or near-term infants. After learning about the cases reported here and because of the lack of information about the prevalence of this behavior in the United States, researchers added the question, "In the past 2 weeks, have you chewed up food and then given it to your infant, so the food was already chewed up before you fed it to your infant?" Separate questionnaires were mailed to parents when the infants were aged 4, 5, 6, 7, 9, 10.5, and 12 months.

Unpublished data from the Infant Feeding Practices Study II[17] indicate that the prevalence of premastication rose from 0.77% (17 of 2203 respondents) at 4 months of age to 10.5% (189 of 1794 respondents) at 10 months of age (Sara Fein, PhD, and Laurence Grummer-Strawn, PhD, written personal communication, 2007). Among the subset of black respondents, the prevalence of premastication was higher than that among other racial and ethnic subgroups and increased as children aged: 5 (6%) of 87 respondents premasticated food for children aged 4 months; 33 (50%) of 66 respondents premasticated food for children aged 10 months. Although the sample was skewed toward white respondents with more education and higher income, the findings suggest a much higher prevalence of premastication than expected and the need for clinical care providers in the United States to be cognizant of this practice.

In a study of complementary infant-feeding practices in China, 62.5% of 104 respondents in various cities reported ever having prechewed food for their children.[16] Among those respondents practicing premastication, 21.5% did so often or very often. They started prechewing food when the child was a median of 8 months old (range: 1–24 months) and stopped at a median of 24 months (range: 5–48 months). Prechewing was also more common when someone other than the parent was involved in feeding the infant.

The association between prechewing food and the transmission of infectious organisms has been documented or hypothesized. The transmission of group A streptococci[18] and hepatitis B virus[15] through premasticated food has been documented; however, both organisms are considerably more infectious than HIV, and as noted, multiple reports have indicated that the risk of oral HIV transmission under ordinary circumstances, such as kissing or sharing household items, is extremely low.[19,20] The feeding of premasticated foods by mothers to infants has been associated with increased risk of *Helicobacter pylori* infection in infants in Burkina Faso[21] and with dental caries in children in southern Asia.[22] Similar transmissions of human herpesvirus 8 in rural Tanzania[23] and Epstein-Barr virus (EBV) in Uganda[24] have been hypothesized. In EBV-endemic regions, some authors have suggested that prechewing food may foster viral transmission to toddlers and may explain, in part, local elevations in the incidence of EBV-associated Burkitt lymphoma in children.[25]

Eating prechewed food, however, may provide health benefits. The premastication of food was protective in univariable but not multivariable analysis against respiratory syncytial virus infection for Alaska Native children aged <6 months.[26] It has also been hypothesized that the feeding of premasticated iron-rich foods may prevent iron deficiency during the first 6 to 12 months of life in resource-limited countries where other sources of iron supplementation are not available during the breastfeeding period.[16] Although the prechewing of food increased bacterial counts in the weaning foods given to infants in northern Thailand, it was suggested that the mother's immunoglobulin A in saliva mixed with the food may reduce the infectivity of these bacteria.[4]

Although our evidence argues in favor of premastication-related HIV transmission facilitated by blood in the mouth of the caregiver and compromised oral mucosa in the child, we acknowledge some limitations. In case 1, phylogenetic evidence linking infection in the child and infection in the premasticating caregiver was lacking because no blood sample was available for the latter. However, the history of premastication and the absence of other modes of transmission are compelling. The possibility of late perinatal seroconversion, for cases 2 and 3 whose mothers were infected with HIV, is extremely unlikely because the results of sequentially performed highly specific tests were negative: in case 3, HIV RNA PCR was performed thrice in the first 6 to 18 weeks of life,[27,28] and in the child of case 2, HIV enzyme-linked immunosorbent assays were performed twice after 18 months of age.[29] HIV-1 RNA testing is reliable for early diagnosis of HIV in infants.[30] Finally, in light of the findings of the Infant Feeding Practices Study II, which indicate that prechewing is common, one might question why, in >10 years, only 3 cases in the United States have been linked to this practice and why no

cases have been reported in resource-limited settings such as Africa, where premastication may be more common than in the United States. A possible explanation is that transmission through breastfeeding makes it difficult to detect premastication-related HIV transmission in resource-limited countries such as Africa; the absence of breastfeeding transmission has allowed us to detect premastication-related transmission in the United States. Premastication-related HIV transmissions are probably rare, requiring a convergence of risk factors affecting both the caregiver and the child. In addition, health care providers are unaware of the practice and have not considered it a potential cause of "late" HIV infection in infants. To our knowledge, no HIV-related MTCT studies with breastfeeding populations have specifically queried caregivers about premastication.[31] The 3 reported cases raise the question as to whether some cases of late pediatric HIV infection reported in MTCT studies and attributed to breastfeeding might have been due in part to the coexisting practice of premastication. Eliciting a history of premastication requires that health care providers be aware that premastication exists and that they are culturally sensitive in asking questions about it. It is crucial to educate caregivers who are infected with HIV about prechewing, because they may be unaware of its potential health risks and may perceive it as a routine, safe, and culturally acceptable practice.

CONCLUSIONS

We hope that our results will prompt additional investigation and the reporting of other potential cases of premastication-related perinatal HIV transmission. Until the risk of prechewing and modifying factors (eg, periodontal disease) are better understood, we recommend that health care providers routinely query children's caregivers and expecting parents who are infected with HIV or at high risk of HIV infection about the practice of premasticating food, that they advise against premastication and that they direct parents and other caregivers to safer, locally available, and accessible feeding options. Translating these recommendations into practice will require cognizance of culturally sensitive issues and potential nutritional consequences linked to premastication. Health care providers should identify the extent to which premastication is practiced in their communities and should notify public health authorities of cases of HIV infection that are potentially linked to premastication. In the United States, such cases should be reported to local health departments according to state surveillance guidelines for HIV/AIDS reporting.

We recognize the potential global implications of our findings. Because infants are fed prechewed food worldwide, we understand that a recommendation against premastication by caregivers infected with HIV should not be made lightly, especially in areas where alternative methods of food preparation are limited and sociocultural beliefs may favor this practice. For example, even in developed nations, providing alternative means for preparing infant food safely, such as blenders, may not eliminate premastication if it has traditional or cultural roots. In resource-limited settings, a risk/benefit analysis will be needed and should take into account the availability of safe feeding practices. Finally, it will be important to determine not only the prevalence of premastication but its contribution to HIV infection in children worldwide in the context of other well-described prenatal, intrapartum, and postnatal risk factors, including breastfeeding.

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医薬品 研究報告 調査報告書

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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)		伊部史, 横幕能行, 服部純子, 間宮均人, 杉浦亙. 第83回日本感染症学会総会学術講演会; 2009 Apr 23-24; 東京.	日本

研究報告の概要

○東海地域におけるHIV-2感染疑い症例の遺伝子学的解析

【目的】HIV-2は西アフリカを中心に感染者数の多い疾患である。HIV-1のように世界的規模で感染は拡大しておらず、本邦では、これまで数例が報告されているのみである。今回、我々は名古屋医療センターにおいて新たにHIV-2の感染が疑われた4例を対象に遺伝子学的診断と分子疫学的解析を実施した。

【方法】血清学的にHIV抗体陽性かつ血中HIV-1 RNAコピー数が検出限度以下を示した4例を対象とした。4例のプロファイルは、外国籍の男性が3例、日本国籍の女性が1例であった。患者末梢血白血球より抽出したDNAを鋳型にnested PCRによりgag (778 bps)およびenv (496 bps)領域の遺伝子増幅を試みた。標的遺伝子の増幅に成功した症例についてはダイレクトシークエンス法で塩基配列を決定したのち、リファレンス株と共に系統樹解析を実施した。

【結果】4例中3例で標的遺伝子の増幅に成功し、遺伝子配列よりHIV-2であることが確認された。これら3例は、全て外国籍の男性症例であり、日本国籍の女性では、いずれの領域も増幅産物を得ることができず確定診断には至らなかった。HIV-2は遺伝子学的にサブタイプAからHの8種類のサブタイプに分類されるが、解析に成功した3例のうち1例はgag、env領域ともにリファレンス株のサブタイプA株と同じ枝に分岐し、サブタイプA株と判定し得た。残り2例は、gag領域ではサブタイプBの近傍への分岐を示し、env領域の解析でも独立した系統群を形成し、両遺伝子領域のみではサブタイプ判定には至らなかった。

【結論】活発化する国際交流は感染症の拡大における地理的な障壁の閾値を低下させている。東海地域において見出されたHIV-2感染症例3例について報告したが、これは我が国においてもHIV-2のスクリーニングを強化しなければならないことを示唆している。

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

報告企業の意見	今後の対応
東海地域においてHIV抗体陽性かつ血中HIV-1 RNAコピー数が検出限度以下を示し、HIV-2感染が疑われた症例4例を分析したところ、3例でウイルス遺伝子の増幅に成功し、HIV-2感染が確認されたとの報告である。 これまで、本製剤によるHIV感染の報告はない。また本製剤の製造工程には、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。さらに最終製品についてHIV-NAT陰性であることを確認している事から本製剤の安全性は確保されていると考える。	今後も情報の収集に努める。なお、日本赤十字社ではHIV抗体検査にこれまでの凝集法と比べてより感度の高い化学発光酵素免疫測定法(CLEIA)を導入したことに加え、20プールNATについてもHIV-2及びHIVグループOの検出が可能な新NATシステムを導入し、陽性血液を排除している。また、輸血感染症対策として、男性と性的接触を持った男性は1年間献血不適としている。

(10)

JRC2009T-042

P-101　血液培養より *Histoplasma capsulatum* を分離したHIV感染症の1例—細菌学的所見を中心に—

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渋谷和俊[5]，佐野文子[6]，亀井克彦[6]，山口恵三[1,2,3]

【目的】ヒストプラズマ症は輸入真菌症のひとつであり，培養陽性率が低いとされている．今回，血液培養より *Histoplasma capsulatum* を分離したHIV感染症の1例を経験したため報告する．

【症例】39歳，タイ人男性．主訴は発熱，発疹，歯肉出血．15年前にタイより来日．4週間前より39～40℃台の発熱が出現，1週間前から歯茎より出血を認め，3日前から出血傾向が増悪したため当院救急外来を受診．精査加療目的にて入院となった．

【入院後経過】HIV抗体陽性．BALFから *Candida albicans* が検出され，β-Dグルカン値の上昇もみられた．IPM，CPFX，FLCZにより治療が開始されたが全身状態は増悪．第6病日に骨髄生検を施行し，病理学的所見で細胞質内に小型類円形の構造物が多数認められ，ヒストプラスマ症が強く疑われた．第8病日よりAMPHにより治療開始したがDICとなり，第25病日，消化管出血のため死亡された．

【血液培養検査】入院時に2セットのボトルが提出された．血培装置で1週間培養を行ったが陰性であったため，ボトルより抽出した培養液沈渣のサブカルチャーを試みた．培養17日目にサブロー寒天に集落の発育を認め真菌陽性との報告をした．同定は27℃と35℃の温度差で二形性を示すこと，集落の形態よりヒストプラズマ属を推定し，血培採取後50日目に報告した．最終的に千葉大学真菌医学研究センターに依頼し，*H. capsulatum* と同定された．一方，ボトルは血培装置で計3週間培養を行ったが陰性であった．

【考察】本症例は臨床側からヒストプラズマ症疑いの情報があったため執拗に培養を行ったことから分離に成功したと思われる．ヒストプラズマ属の培養は27℃で4週間まで観察することが推奨されているが，一般細菌用の血培ボトルは5～7日しか培養を行わないため本菌をはじめとする培養に時間を要する真菌を疑うときは繰り返し血培装置に充填するか，培養液沈渣を用いてサブカルチャーを行う必要があると考えられた．

P-102　東海地域におけるHIV-2感染疑い症例の遺伝子学的解析

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杉浦　亙

【目的】HIV-2は西アフリカを中心に感染者数の多い疾患である．HIV-1のように世界的規模で感染は拡大しておらず，本邦では，これまで数例が報告されているのみである．今回，我々は名古屋医療センターにおいて新たにHIV-2の感染が疑われた4例を対象に遺伝子学的診断と分子疫学的解析を実施した．

【方法】血清学的にHIV抗体陽性かつ血中HIV-1 RNAコピー数が検出限度以下を示した4例を対象とした．4例のプロファイルは，外国籍の男性が3例，日本国籍の女性が1例であった．患者末梢血白血球より抽出したDNAを鋳型にnested PCRによりgag (778 bps) およびenv (496 bps) 領域の遺伝子増幅を試みた．標的遺伝子の増幅に成功した症例についてはダイレクトシークエンス法で塩基配列を決定したのち，リファレンス株と共に系統樹解析を実施した．

【結果】4例中3例で標的遺伝子の増幅に成功し，遺伝子配列よりHIV-2であることが確認された．これら3例は，全て外国籍の男性症例であり，日本国籍の女性では，いずれの領域も増幅産物を得ることができず確定診断には至らなかった．HIV-2は遺伝子学的にサブタイプAからHの8種類のサブタイプに分類されるが，解析に成功した3例のうち1例はgag，env領域ともにリファレンス株のサブタイプA株と同じ枝に分岐し，サブタイプA株と判定し得た．残り2例は，gag領域ではサブタイプBの近傍への分岐を示し，env領域の解析でも独立した系統群を形成し，両遺伝子領域のみではサブタイプ判定には至らなかった．

【結論】活発化する国際交流は感染症の拡大における地理的な障壁の閾値を低下させている．東海地域において見出されたHIV-2感染症例3例について報告したが，これは我が国においてもHIV-2のスクリーニングを強化しなければならないことを示唆している．

別紙様式第2-1

No. 19

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. 7. 9	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)		47 news. Available from: http://www.47news.jp/CN/20090 6/CN2009062701000591.html.	日本

研究報告の概要

○白血病ウイルス感染者108万人(推計) 大都市圏で割合増

母乳を通じて母子感染し、白血病などを引き起こす可能性がある成人T細胞白血病ウイルス(HTLV-1)について厚生労働省研究班が約20年ぶりに実施した調査で、感染者の地域別割合がもともと高かった九州で減少し、関東や中部、近畿の大都市圏で増加したことが27日、分かった。国内の感染者数は約108万人と推計。旧厚生省研究班が1988～90年度にまとめた調査の約120万人と比べ大きな変化はなかった。これまで全国的な対策は取られておらず、子供への感染を防ぐ取り組みが急務となりそうだ。研究班班長の山口一成国立感染症研究所客員研究員は大都市圏での割合増加について、感染者が多い九州からの人の移動が背景にあると指摘。「妊婦への抗体検査や授乳指導を実施している自治体は一部に限られ、感染者総数もあまり減少していない」と話した。

HTLV-1はATLと呼ばれるタイプの白血病や、歩行障害などが出る脊髄症(HAM)の原因となる。ATLの発症率は3～5%。根本的な治療法はなく、年間約千人が亡くなっている。

今回の調査は、2006～07年に初めて献血した全国の約119万人を対象に実施、3787人の感染が確認された。感染者の地域別割合は、九州が前回調査の50.9%から41.4%に減少。一方、関東は17.3%(前回10.8%)、中部8.2%(同4.8%)、近畿20.3%(同17.0%)で、いずれも前回より増加した。

報告企業の意見	今後の対応
2006～07年に初めて献血した人を対象に行った調査の結果、全国の成人T細胞白血病ウイルスの感染者数は約108万人と推計され、感染者の地域別割合はもともと高かった九州で減少し、関東や中部、近畿の大都市圏で増加したことが分かったとの報告である。 これまで、本製剤によるHTLV-1感染の報告はない。本製剤の製造工程には、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。本製剤の安全性は確保されていると考える。	今後も引き続き、新たなウイルス等による感染症の発生状況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

(二)

白血病ウイルス感染者108万人　大都市圏で割合増

母乳を通じて母子感染し、白血病などを引き起こす可能性がある成人T細胞白血病ウイルス（HTLV1）について厚生労働省研究班が約20年ぶりに実施した調査で、感染者の地域別割合がもともと高かった九州で減少し、関東や中部、近畿の大都市圏で増加したことが27日、分かった。

国内の感染者数は約108万人と推計。旧厚生省研究班が1988～90年度にまとめた調査の約120万人と比べ大きな変化はなかった。これまで全国的な対策は取られておらず、子供への感染を防ぐ取り組みが急務となりそうだ。

研究班班長の山口一成国立感染症研究所客員研究員は大都市圏での割合増加について、感染者が多い九州からの人の移動が背景にあると指摘。「妊婦への抗体検査や授乳指導を実施している自治体は一部に限られ、感染者総数もあまり減少していない」と話した。

HTLV1はATLと呼ばれるタイプの白血病や、歩行障害などが出る脊髄症（HAM）の原因となる。ATLの発症率は3～5%。根本的な治療法はなく、年間約千人が亡くなっている。

今回の調査は、2006～07年に初めて献血した全国の約119万人を対象に実施、3787人の感染が確認された。

感染者の地域別割合は、九州が前回調査の50・9%から41・4%に減少。一方、関東は17・3%（前回10・8%）、中部8・2%（同4・8%）、近畿20・3%（同17・0%）で、いずれも前回より増加した。

2009/06/27 16:03 【共同通信】

ホーム 共同ニュース

■47ニュース アクセスランキング一覧へ

別紙様式第2-1

No. 12

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. 8. 18	該当なし	

一般的名称	新鮮凍結人血漿	研究報告の公表状況		公表国
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社)		Euro Surveill. 2009 May 14;14(19).	オランダ

研究報告の概要

○オランダ南部におけるQ熱の持続的集中的伝播、2009年

オランダは、2007年と2008年のアウトブレイク後再びQ熱報告の急増に直面している。もっとも影響が大きいのは大規模なヤギ農場が集中しているNoord Brabant県であり、流産の増加している農場が発生源と疑われる。複数の専門分野にわたる大規模な調査研究により、疾患の伝播や予防手段に関する知見が得られることが期待される。

Q熱症例数は2009年4月以降急増し、1月1日から5月11日までの間に345例(可能性例13例を含む)が報告された。11例は2008年、1例は2007年に発症していたため、2009年に発症した症例は合計333例という結果となった。男女比は約1.7:1で、年齢の中央値は49才(38-61才)であった。過去の2年と比べて4-5月に患者数が急増しており、流行の規模は2008年と同程度以上になることが示唆されている。ほとんどの患者が、2007年、2008年と同様Noord Brabant県民であったが、感染区域に拡大傾向が見られている。

主な症状は肺炎で、2008年に報告された患者では、545名が肺炎、33名が肝炎、115名が他の発熱性疾患を発症した。2009年の症例のうち、データの得られた226例中59例(26%)が入院した。これは2008年度と同程度の割合だが、2007年(49%)よりは少なかった。

Noord Brabant県を中心に、少なくとも10件の独立した流行クラスターがあることが明らかになってきた。一部のクラスターでは、家畜のQ熱が発生し流産が増加している小型反芻動物農場との明確な疫学的関連性があった。動物のワクチン接種キャンペーンが始まっており、2010年には効果を発揮する見込みである。

報告企業の意見	今後の対応
オランダ南部においてQ熱の患者が急増しており、一部では家畜のQ熱が発生している農場との疫学的関連性があったとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

(12)

Sustained intensive transmission of Q fever in the south of the Netherlands, 2009

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3. Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands
4. Municipal Health Service South Limburg, Sittard-Geleen, the Netherlands
5. Municipal Health Service Brabant-Southeast, Helmond, the Netherlands
6. Municipal Health Service "Hart voor Brabant", 's Hertogenbosch, the Netherlands

The Netherlands is again facing a sharp increase in Q fever notifications, after the unprecedented outbreaks of 2007 and 2008. The most affected province of Noord Brabant has a high density of large dairy goat farms, and farms with abortion waves have been incriminated. Mandatory vaccination of small ruminants has started and should have an effect in 2010. A large multidisciplinary research portfolio is expected to generate better knowledge about transmission and additional control measures.

Introduction

Q fever is a zoonosis caused by the obligate intracellular bacterium *Coxiella burnetii*. Cattle, sheep and goats are the primary animal reservoir, but the causative agent has also been noted in many other animal species. Infected goats and sheep may abort, mainly in late pregnancy. The bacterium is shed in urine, faeces, milk and in especially high concentrations in placentas and birth fluids of infected animals. Bacteria are transmitted to humans mainly through the aerosol route, resulting in subclinical infection, a flu-like syndrome with abrupt onset of fever, pneumonia or hepatitis, after an incubation period of two to three weeks [1]. People with underlying conditions, especially heart valve lesions, are more susceptible to developing chronic Q fever. Endocarditis, the most common form of chronic Q fever is estimated to occur in about 1% of acute Q fever cases.

Since 1978, when Q fever in humans became a notifiable disease in the Netherlands, until 2006, the number of notifications had ranged between 1 and 32 cases annually, with an average of 17 cases per year [2]. However, in 2007, Q fever emerged as an important human and veterinary public health challenge with large epidemics in the southern part of the Netherlands [3]. In 2007, 168 human cases were notified and in 2008 exactly 1,000 human cases were registered (Figure 1). Notification criteria for acute Q fever are a clinical presentation with at least fever, or pneumonia, or hepatitis and confirmation of the diagnosis in the laboratory. Currently, the laboratory criteria are a fourfold rise in IgG antibody titre against *C. burnetii* in paired sera or the presence of IgM-antibodies against phase II antigen. Identification of *C. burnetii* in patient material with a PCR test will soon be added to the notification criteria. Notification of probable cases, defined as clinical signs with a single high antibody titre is voluntary.

Current situation

From April 2009, a sharp increase in Q fever was observed again, and a total of 345 cases (including 13 probable) were notified between 1 January and 11 May 2009 (Figure 1). For 11 cases, the date of illness onset was in 2008 and one case fell ill in 2007, resulting in a total of 333 cases with confirmed or presumed illness onset in 2009. The overall male-to-female ratio for these 333 cases was 1.7:1 with a median age of 49 years (IQR 38-61 years).

The epidemic curve for 2009 shows an even steeper increase in case numbers in April-May, than in the previous two years, suggesting that an epidemic of at least the same magnitude as the one in 2008 is imminent. While most cases reside in the same region in the province of Noord-Brabant as the cases reported in 2007 and 2008 (see map in reference 3), the geographic area seems to be expanding (Figure 2).

Clinical features and diagnostics

Pneumonia is the predominant clinical presentation of the Q fever cases in the Netherlands. For those patients notified in 2008 for whom clinical details were available, 545 presented with pneumonia, 33 with hepatitis, and 115 with other febrile illness (data not yet analysed in detail). Of the 226 cases in 2009 where data regarding hospitalisation were available, 59 (26%) had been admitted to a hospital, a percentage comparable to figures in 2008, but lower than the proportion of patients hospitalised in 2007 (49%). Clinical follow-up of patients that were diagnosed with acute Q fever in 2007, shows that Q fever is not always a mild disease of short duration, as many cases still suffered from persisting fatigue several months after disease onset [4]. We have no clear information about the occurrence of other chronic sequelae, such as endocarditis at this stage.

The medical microbiology laboratories in the affected region have jointly formulated diagnostic recommendations. Cases are currently diagnosed with immunofluorescence assays (Focus

Diagnostics), in-house complement fixation tests or ELISA. Real-time polymerase chain reaction (PCR) tests were developed by eight medical microbiology laboratories and the most sensitive (98%) PCR has been selected and has proven a valuable additional tool for early diagnosis of acute Q fever in the time window before seroconversion.

Increased alertness of general practitioners together with easy availability of diagnostic services certainly has an impact on the number of notifications. The current epidemic curve based on week of notification reflects a more real time situation than in previous years, as the interval between date of illness onset and date of diagnosis has decreased from a median of 77 days in 2007 (IQR 40-121) and 29 days (IQR 19-45) in 2008 to 17 days in 2009 (IQR 12-24 days).

Separate clusters with multiple sources

It is becoming increasingly clear that the overall outbreak consists of at least 10 separate clusters with multiple sources, mainly in the province of Noord Brabant. For some clusters a clear epidemiological link could be established to small ruminant farms with clinical Q fever cases in animals presented as abortion waves. For other clusters such a link was less obvious. An example of the latter is a medium sized city (87,000 inhabitants) that experienced a second Q fever outbreak in 2009 similar to the one in 2008. In 2008, a dairy goat farm with abortions due to Q fever was suspected as the source, but in 2009 there were no veterinary notifications from the area. The 73 notified human cases residing in the city were clustered in the same part of the city as the cases that were notified in 2008. It remains unclear whether the same source is involved, whether the bacteria have persisted and survived in the local environment, whether the primary source in 2008 has resulted in secondary sources in 2009, or whether there is increased awareness among health professionals in this part of the city based on the 2008 experience.

In March 2009, the Animal Health Service reported a Q fever-positive farm in the province of Limburg with more than a thousand goats. The place also serves as a care farm for young people with mental disabilities who work there as part-time farmhands. Prompted by this notification, the municipal health service (MHS) South Limburg performed active laboratory screening by ELISA of the individuals affiliated to this goat farm. The screening, which involved a total of 96 people, has resulted in 28 notified symptomatic cases to date.

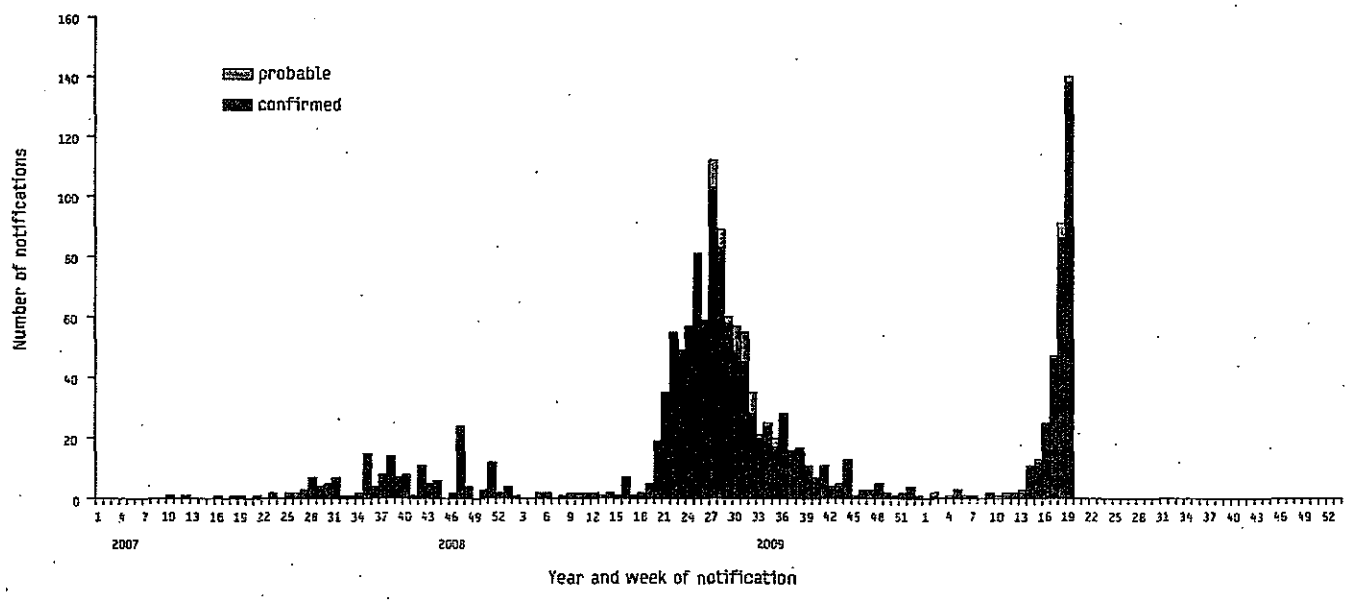
Veterinary situation

The total number of registered small ruminant farms in the Netherlands is 52,000, of which 350 are professional dairy goat farms with more than 200 adult goats and 40 are professional dairy sheep farms. In 2005, Q fever was diagnosed for the first time as a cause of abortion at a dairy goat farm, using immunohistochemistry on sections of placenta [5]. A second case was diagnosed later in 2005. In 2006, 2007 and 2008, six, seven and seven new cases at dairy goat farms were confirmed, respectively, mainly in the same area where human cases occurred. In the same period, two cases of abortion caused by *C. burnetii* were confirmed at dairy sheep farms, one in the southern and one in the northern part of the country but these two cases do not seem to be related to human cases. Analyses of abortion outbreaks showed that the average number of goats per farm was 900 of which 20% aborted, ranging from 10-60%. The average number of sheep on both infected sheep farms was 400 and the abortion rate was 5%.

Abortion outbreaks before June 2008 were reported on a voluntary basis to the Animal Health Service and also confirmed by immunohistochemistry. Since June 2008, notification of Q fever in goats and sheep is mandatory in the Netherlands. There is a legal requirement for farmers and their private veterinary surgeons to notify the occurrence of abortion in small ruminants held in deep litter houses. For large farms (>100 animals) the notification

FIGURE 1

Q fever notifications by week of notification, 1 January 2007 - 11 May 2009, the Netherlands (2007: n=168, 2008: n=1000, 2009 [week 1-week 19]: n=345)



criterion is an abortion wave defined as an abortion percentage higher than 5% among pregnant animals. For smaller holdings, a criterion of three or more abortions in a 30-day period is used.

From January to April 2009, this new regulation has led to notification of three dairy goat farms with clinical cases of Q fever. One farm is located in the province of Overijssel (notified in February), one in the south of the province of Limburg (notified in March), and one in the province of Noord-Brabant (notified in April).

This veterinary notification can potentially facilitate the detection of related human cases or clusters. Veterinarians, physicians and the public are informed through targeted mailings, publications and the media. The exact location of animal farms with clinical Q fever is now reported to the municipal health service. In February 2009, a nationwide stringent hygiene protocol became mandatory for all professional dairy goat and sheep farms, independent of Q fever status.

Vaccination campaigns

In the fall of 2008, a voluntary vaccination campaign was implemented in the province of Noord Brabant. In total, about 36,000 small ruminants were vaccinated in an area with a radius of 45 kilometer around Uden, a small town in the centre of the high-risk area.

Another, mandatory vaccination campaign led by the Animal Health Service (GD) started on 21 April 2009. From April to October 2009, 200,000 small ruminants will be vaccinated in an area which includes the province of Noord-Brabant and parts of the provinces of Gelderland, Utrecht and Limburg.

Ongoing research

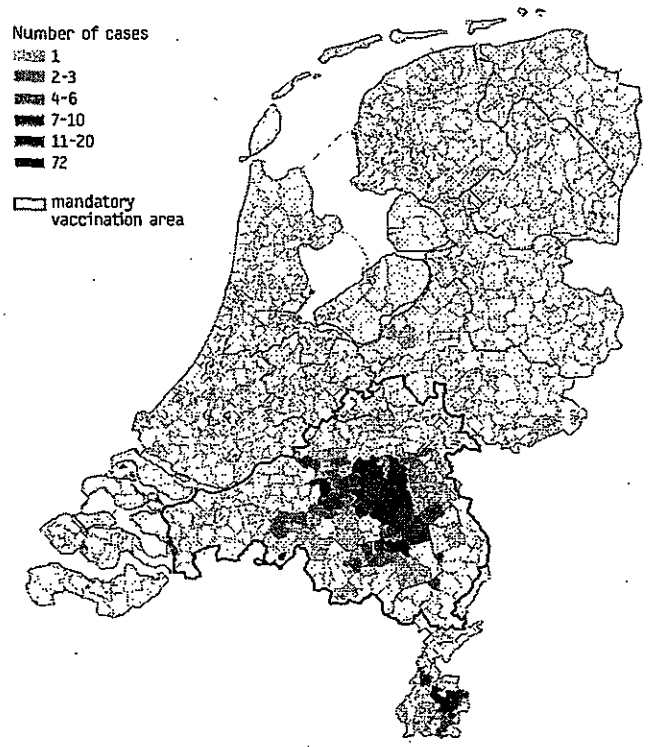
Ongoing studies address the factors involved in the 2008 epidemic at a national, regional and local level, the efficacy of the 2008 voluntary vaccination campaign in small ruminants and the nationwide occurrence of *C. burnetii* antibodies in the community and in small ruminants. From the human epidemiological perspective, a case control study is currently underway in the two main affected MHS regions of 2009, 'Hart voor Brabant' and Brabant-Southeast. Routinely collected sera of pregnant women from the affected regions over the period June 2007 to July 2008 are retrospectively screened for Q fever to study the effect of infection on pregnancy outcome (registered in a national database). An integrated human-veterinary study was started, in which small ruminant farmers and their animals will be screened for presence of *C. burnetii* antibodies. In addition, environmental samples will be obtained from a subset of these farms and the role of particulate matter in relation to *C. burnetii* transmission will be further investigated.

Conclusion

For the third consecutive year the Netherlands is facing a large outbreak of Q fever. The new upsurge in Q fever cases in 2009 is alarming. The mandatory vaccination campaign among small ruminants that was started in April 2009, if effective, is expected to reduce the occurrence of abortion waves and excretion of *Coxiella* in the lambing season 2010. There is a large portfolio of ongoing multidisciplinary research, but it will take some time before results become available that eventually will lead to the implementation of extended and improved control measures.

FIGURE 2

Notified cases of acute Q fever in the Netherlands by three-digit postal code area, 1 January – 11 May 2009 (n=344*). The black line indicates the mandatory vaccination area covering the province of Noord Brabant and parts of the provinces of Gelderland, Utrecht, and Limburg.



Source: OSIRIS notification system. Map compiled by Ben Bom, Expertise Centre for Methodology and Information Services, RIVM
* For one case the information on postal code is missing

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別紙様式第2-1
番号15

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2009年6月29日	新医薬品等の区分	厚生労働省処理欄

一般的名称	①②③④人血清アルブミン ⑤乾燥濃縮人血液凝固第Ⅷ因子 ⑥⑦乾燥濃縮人血液凝固第Ⅸ因子	研究報告の公表状況	FDA(Vaccines, Blood & Biologics)/2009/06/12	公表国 アメリカ
販売名 (企業名)	①献血アルブミン25%静注5g/20mL「ベネシス」（ベネシス） ②献血アルブミン25%静注12.5g/50mL「ベネシス」（ベネシス） ③献血アルブミン5%静注5g/100mL「ベネシス」（ベネシス） ④献血アルブミン5%静注12.5g/250mL「ベネシス」（ベネシス） ⑤コンコエイトーHT（ベネシス） ⑥クリスマシンM静注用400単位（ベネシス） ⑦クリスマシンM静注用1000単位（ベネシス）			

研究報告の概要

FDAは、全血および成分血の製造施設、ヒト細胞・組織・それら由来製剤(HCT/Ps)のドナーの適性判定施設において、Trypanosoma cruzi（T. cruzi）抗体を検出するための酵素免疫反応試験（ELISA）の承認申請（BAL）がFDAにより承認されたことを通知する。この検査は輸血に使用される全血および成分血、およびHCT/Pドナー（生体および死後（心停止））を含む個別ドナー血漿および血清サンプルにおけるT. cruzi抗体検出により、T. cruziの伝播リスクを低減させることを目的とする。このガイダンス文書は、分画製剤用原料血漿の採集には適用されない。FDAはこのガイダンスの最終版発行後1年以内にこのガイダンスに記載の推奨事項を実施するよう推奨する。
1989年9月のBlood Products Advisory Committee（BPAC）の会合で、委員会は適当な検査が利用可能になったとき、全血および成分血のドナーにシャーガス病の検査をすることを勧めた。2006年12月、FDAは血液及びHCT/Psドナーにおける T. cruzi抗体の検出のためのELISA検査システムを製造業者1社に許可した。2007年1月の末以来、米国血液センターの多くは、この許可された測定法を使用してドナーを検査した。2009年2月、FDAは死んだ（心停止）HCT/Psドナーにおける、T. cruzi抗体の検出のためにこのELISA検査システムを認可した。
1990年代半ばの米国の血液ドナーの血清陽性率は1/5400～1/25000であった。しかし、最近の研究ではこれより増加していることを示唆している。例えば、Los Angeles大都市圏で最近では1/2000であることがわかった。
伝播経路として垂直感染、経口感染、粘膜感染、胎盤感染があり、適切なスクリーニング及び/又は検査を実施する有用性について報告をすることが記載されている。

報告企業の意見	今後の対応
米国における全血、血液成分及びHCT/Psにおけるトリパノソーマ症感染伝播のリスク低減のためのドナースクリーニングについての業者向けガイダンス(案)である。 血漿分画製剤からのトリパノソーマ原虫伝播の事例は報告されていない。また、万一原料血漿にTrypanosoma cruziが混入したとしても、除菌ろ過等の製造工程において十分に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。

使用上の注意記載状況・その他参考事項等

代表として献血アルブミン25%静注5g/20mL「ベネシス」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人アルブミンを精製し、アルブミン濃度25w/v%に調整した製剤であり、ウイルス不活化を目的として、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。

(13)

Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

DRAFT GUIDANCE

This guidance document is for comment purposes only.

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

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

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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TABLE OF CONTENTS