ELISA were tested in the WNV neutralization assay, the "gold standard" for antibody detection, to confirm a past infection. Most of the pre-selected specimens did not inhibit WNV infection in cell culture at all or did so only at a low level (log $TCID_{50} < 1.5$). The titer of 13 additional samples was between $\geq 1.5$ and $<2$.

Only four blood donor samples exhibited a log titer of $>2$, which was similar to those titers we determined for different clinically confirmed WNV positive sera from the US (Table I). We interviewed the four anti-WNV positive blood donors to evaluate if these putative WNV infections occurred in Germany or Europe or if they might be associated with WNV-endemic countries. One of the four donors had never left Europe, but had visited South and East Europe; another donor had only stayed outside Germany in Turkey. The other two donors had traveled abroad to the USA and Africa. We therefore cannot exclude that singular sporadic and asymptomatic WNV infections may have occurred in Europe and the Middle East. However, WNV prevalence among German blood donors is overall very low; in our study, only 0.03% (95% CI: 0.01–0.07%) of blood donors that were tested were confirmed positive for anti-WNV antibodies by our approach.

### WNV-RNA Incidence

For WNV infections, a diagnostic window of only few days (until detection of anti-WNV) has been described during which viral RNA may be detectable. With a WNV-RNA concentration range described from <50 copies/ml up to $10^5$ copies/ml [Busch et al., 2005b], the short viremia is at a moderate level when compared to the respective figures for other blood-borne viral infections like HCV (3 months, $10^5$–$10^8$ IU/ml) or HIV (4 weeks, $10^2$–$10^6$ IU/ml) [Lelie et al., 2002].

WNV-RNA incidence in Germany was analyzed in minipools comprised of eight blood donations collected during Summer 2005 and using the highly sensitive Chiron Procleix WNV NAT [Gallian et al., 2005]. Since different WNV strains were described as circulating in Central Europe [Bakonyi et al., 2005, 2006], we investigated whether the Procleix assay detects all available WNV strains. A panel from an external quality assurance study [Niedrig et al., 2006] was retrospectively analyzed. The result confirmed the capability of the Procleix assay to detect WNV lineage 1 and 2 with high sensitivity (data not shown).

No minipools were confirmed positive for WNV-RNA after screening of 1,247 minipools (equal to 9,976 donations). Negative NAT results were also obtained for all individually tested samples from a population that was at increased risk for blood-transmitted infections [i.e., intravenous drug users (IVDUs, n = 78)], or for plasma samples of serologically anti-WNV-reactive blood donors (n = 198).

This outcome is in accordance with the recent WNV-RNA screening results of more than 60,000 Dutch blood donors [Koppelman et al., 2006]. Regardless, blood donors who had just recently visited a WNV endemic country (e.g., the USA) are excluded from the actual donation as a precautionary measure in German blood banks.

### Plasma Derivatives

Plasma derivatives (e.g., immunoglobulin preparations, albumin, factor concentrates) may enter the European market with source materials collected in different parts of the world. We were interested in the question of whether WNV-RNA is detectable in aliquots of manufacturing plasma pools.

Some of the plasma pools with plasma of US origin tested positive for WNV RNA by the qualitative NAT assay. The viral load in these plasma pools was determined in the range between 57 and 837 copies/ml, with a median of 351 copies/ml. Each of these pools was composed of several thousand plasma units. Assuming that WNV input in these pools originates from only few donors, WNV concentration of $10^5$–$10^6$ copies/ml are calculated for some individual plasma units. Such high WNV-RNA concentrations have been described for the diagnostic window phase in few cases. However, WNV input into plasma pools from lower viremia cases may be not detected due to the dilution effect though they are expected to be much more frequent and representative for the early infection phase.

Several studies proved that inactivation steps commonly used during the manufacture of plasma derivatives, such as pasteurization for human albumin, S/D treatment for IVIG and FVIII inhibitor-bypassing activity, and incubation at low pH for IVIG, should be sufficient to inactivate enveloped viruses present in source materials [Kreil et al., 2003]. We comparatively investigated the efficacy of pasteurization with regards to WNV and model viruses for enveloped viruses. In these experiments WNV inactivation kinetics were similar between WNV and the two model viruses, BVDV and SFV. This result confirmed the validity of predictions based on model viruses if chosen appropriately. It allowed the conclusion that moderate WNV concentrations in plasma pools should not pose an infection risk to recipients if virus inactivation procedures are included in the manufacturing process of these biological medicinal products.

## CONCLUSION

There is currently no indication that WNV could cause an epidemic in Europe similar to that in the USA during the recent years, although temporally and regionally limited outbreaks of WNV infections in humans and horses have been observed in Europe since the 1950s. In contrast to North America, Europe has had direct vector contact with WNV endemic areas in Africa for a long time, via migratory birds, for example. This may have resulted in natural herd immunity in birds. In America, a highly pathogenic WNV strain was imported in 1999 into a virgin territory, meeting a bird population without herd immunity. Environmental factors, such as climate change or global warming and the increasing

mobility of people, may enhance the emergence of new viruses. Therefore, continuous surveillance is an important tool to protect public health and the safety of the blood supply.

## ACKNOWLEDGMENTS

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別紙様式第2-1

No. 27

# 医薬品 研究報告 調査報告書

| 識別番号・報告回数 | | | 報告日 | 第一報入手日 | 新医薬品等の区分 | 機構処理欄 |
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| 一般的名称 | (製造承認書に記載なし) | 研究報告の公表状況 | ProMED 20071130-3869, 2007 Nov 30. 情報源:[1]World Health Organisaation (WHO), CSR, Disease Outbreak News, 2007 Nov 30. [2]Agence France Press (AFP) report, 2007 Nov 30. | 公表国 |
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| 販売名(企業名) | 合成血「日赤」(日本赤十字社)<br>照射合成血「日赤」(日本赤十字社)<br>合成血-LR「日赤」(日本赤十字社)<br>照射合成血-LR「日赤」(日本赤十字社) | | | ウガンダ |

**研究報告の概要**

○ウガンダにおけるエボラ出血熱アウトブレイク
[1]ウガンダの保健省は西部のBundibugyo地区でのエボラ出血熱アウトブレイクを確認した。2007年11月28日時点で疑い症例51例、うち死亡例16例が報告されている。報告例には医療関係者の感染も3例含まれており、このうち1例は死亡している。国立研究所および米国疾病対策予防センター(CDC)の実施した臨床検査により、患者検体からエボラウイルスの新種の存在が確認された。現地調査によると、アウトブレイクは2007年9月から始まっていた可能性がある。同国保健省の対策委員会、WHOや他の国際機関は協力して対応に当たっていく。
[2]2007年11月30日、ウガンダ保健省は、同国西部で51人が感染し、少なくとも16人が死亡したエボラウイルスは未知のウイルス株であると発表した。CDCの検査施設に送られた患者の血液及び組織検体を分析したところ、これまでウガンダの他の地区やコンゴ民主共和国で流行していたエボラウイルスの株とは異なった性質が見られた。専門家によると、これまでの株は血管の内膜を破壊することで出血を引き起こし、ショックによって患者を死に至らしめるが、新しい株では出血はそれほど多くなく、患者は高熱を発症後に死亡するとのことである。当局は疫学やウイルス学の専門家を集めて同地区の疾患を監視し、高熱や腹痛、嘔吐、紅斑を発症した人に注意している。

| 報告企業の意見 | 今後の対応 |
|---|---|
| ウガンダ西部のBundibugyo地区でエボラ出血熱の集団発生が見られ、エボラウイルスの新種の存在が確認されたとの報告である。 | 日本赤十字社は、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。今後も引き続き情報の収集に努める。 |

**使用上の注意記載状況・その他参考事項等**

合成血「日赤」
照射合成血「日赤」
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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

Back

**Archive Number** 20071130.3869
**Published Date** 30-NOV-2007
**Subject** PRO/AH/EDR> Ebola hemorrhagic fever - Uganda: (Bundibugyo), WHO

EBOLA HEMORRHAGIC FEVER - UGANDA: (BUNDIBUGYO), WHO
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A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

[1]
Date: Fri 30 Nov 2007
Source: World Health Organisaation (WHO), CSR, Disease Outbreak News [edited]
<http://www.who.int/csr/don/2007_11_30a/en/index.html>

Ebola haemorrhagic fever in Uganda
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The Ministry of Health (MoH), Uganda, has confirmed an outbreak of Ebola haemorrhagic fever, in Bundibugyo District, western Uganda. As of Thu 28 Nov 2007, 51 suspected cases, including 16 deaths have been reported. Among the reported cases, 3 health care workers were also infected, including one fatality. The patients are being hospitalized at Kikyo and Bundibugyo.

Laboratory analysis undertaken at the National Reference Laboratories and the Centres for Disease Control and Prevention (CDC), Atlanta, USA, has confirmed the presence of a new species of Ebola virus in samples taken from cases associated with the outbreak.

Based on initial field investigations, the MoH/WHO Country office has reported that the outbreak might have been ongoing since September 2007. A national task force comprising MoH, WHO and other international partners in the field, is coordinating the response to this outbreak. WHO Country office is assisting the MOH national field team and the District health officials.

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Communicated by:
ProMED-mail Rapporteur Marianne Hopp

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[2]
Date: Fri 30 Nov 2007
Source: Agence France Press (AFP) report [edited]
<http://afp.google.com/article/ALeqM5j8JhykvCqpuWN9lWD4ZjGnYZeA_g>

Uganda's Ebola outbreak is new strain
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A lethal Ebola virus that has killed at least 16 people and infected 51 others in western Uganda is a previously unknown strain, health authorities said Friday [30 Nov 2007]. Analysis on victims' blood and tissue samples sent to the Atlanta-based Centers for Disease Control's pathogens laboratory behaved differently from previous known strains of Ebola, they said. "It is a new type of strain. It is different from the one we suffered in Gulu and also different from the one that was reported in the Democratic Republic of Congo," said Sam Okware, who chairs Uganda's national hemorrhagic fever task force. The 1st Ebola case was reported on 10 Nov 2007 in Bundibugyo district on the border with the Democratic Republic of Congo, where 3

patients are currently in an isolation ward.

Virologists say previous strains destroyed the linings of blood capillaries and vessels, prompting fluids to drain out of the circulatory system through the body's orifices and pores, killing the victim through shock. But there is not much bleeding in the new strain that appears to kill its victims after provoking a high fever, they say.

Authorities have assembled epidemiologists and virologists in the affected district to monitor the disease. "We have put our people on alert for anyone who is complaining of fever, abdominal pain, vomiting and has developed rashes," Okware said, referring to the early symptoms of the disease caused by the new strain.

An outbreak of Ebola, a highly contagious disease that can have fatality rates as high as 90 percent, killed at least 170 people in northern Uganda's Gulu district in 2000. A similar outbreak has killed at least 26 people in the West Kasai region of the Democratic Republic of Congo in recent weeks, according to the country's Health Minister Victor Makwenge Kaput.

It spreads by direct human contact, especially through infected blood. The Ebola virus was first identified in 1976 in Sudan and in a nearby region of Democratic Republic of the Congo (then Zaire). Outbreaks of Ebola have also occurred in the Ivory Coast and Gabon.

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[The difference in symptoms of the disease associated with this new strain of Ebola virus, and its less hemorrhagic presentation, may account in part for the delay in identifying the causes of the outbreak. On the basis of the WHO report it must be presumed that the disease was present in the region for several weeks prior to recognition of the 1st case on 10 Nov 2007.

An interactive map of the Bundibugyo region of Western Uganda is available at: <http://www.maplandia.com/uganda/bundibugyo/>. - Mod.CP]

[see also:
Hemorrhagic fever - Uganda (04): (Bundibugyo), Ebola confirmed 20071130.3859
Hemorrhagic fever - Uganda (03): (Bundibugyo) 20071121.3775
Hemorrhagic fever - Uganda (02): (Bundibugyo), Marburg NOT 20071116.3718
Hemorrhagic fever - Uganda (Bundibugyo): Marburg susp., RFI 20071114.3697
Marburg hemorrhagic fever - Uganda (06): new case 20071002.3257
Marburg hemorrhagic fever - Uganda (05) 20070817.2697
Marburg hemorrhagic fever - Uganda (04), WHO 20070814.2656
Marburg hemorrhagic fever - Uganda (03) 20070810.2609
Marburg hemorrhagic fever - Uganda (02) 20070804.2533
Marburg hemorrhagic fever - Uganda 20070803.2514
Viral hemorrhagic fever - Uganda (Kamwenge): Marburg conf. 20070801.2490
Viral hemorrhagic fever - Uganda (Kamwenge): Marburg susp., RFI 20070801.2475
2001
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Ebola hemorrhagic fever - Uganda: postscript 20011019.2576]
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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) | 合成血「日赤」(日本赤十字社)<br>照射合成血「日赤」(日本赤十字社)<br>合成血-LR「日赤」(日本赤十字社)<br>照射合成血-LR「日赤」(日本赤十字社) | | | | | |

**研究報告の概要**

○イタリアでのチクングニヤウイルス感染症:温帯地域におけるアウトブレイク

背景:ヤブカ類(Aedes spp.)によって伝播されるチクングニヤウイルス(CHIKV)は、近年インド洋諸島やインド亜大陸において複数のアウトブレイクを引き起こした。ここではイタリアでのアウトブレイクを報告する。

方法:イタリア北東部の隣りあった2つの村で原因不明の発熱性疾患が多数報告された後、主要感染源と伝播形態を特定するためのアウトブレイク調査を実施した。能動的サーベイランスシステムも導入した。臨床症例定義は、発熱と関節痛の発症とした。血液検体を採取、PCRと血清学的検査を行って病原体を特定した。現地で採取した蚊にもPCRを実施した。CHIKV E1領域の系統発生学的解析を行った。

知見:ヒトおよび蚊由来検体の分析により、当該アウトブレイクはCHIKVによるものと判明した。2007年7月4日から9月27日までにCHIKV感染症例205例が特定された。推定初発症例は、当該の村に親類を訪ねた際に発症したインドの男性とされた。系統発生学的解析では、イタリアで特定された株とこれより前にインド洋諸島のアウトブレイク時に特定された株との間に高い相同性が示された。ほぼ全例とも症状はかなり軽度で、死亡報告は1例のみであった。

考察:非熱帯地域における今回のCHIKV感染症アウトブレイクは、ある意味予期せぬ事態であり、グローバル化時代における新興感染症の脅威に対する準備と対策の必要性が強く示唆される。

| 報告企業の意見 | 今後の対応 |
|---|---|
| 2007年7月4日から9月27日までにイタリアにおいてチクングニヤウイルス感染症例205例が集団発生し、グローバル化時代における新興感染症の脅威に対する準備と対策の必要があるとの報告である。 | 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。国内でチクングニヤ熱が確認されたため、渡航歴確認の徹底を図っている。また、チクングニヤ熱の既往歴がある場合、治癒後6ヵ月間は献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する情報の収集に努める。 |

**使用上の注意記載状況・その他参考事項等**

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