time of scrapie exceeded the natural life span of these mice.

All clinically unaffected *tga20* indicator mice were killed at ≥200 dpi. Histopathological and immunoblot analyses confirmed scrapie in all clinically diagnosed *tga20* mice and excluded it from all others (Fig. 2, A to C, and fig. S5C). Phosphotungstate-mediated concentration of PrP^{Sc} from 1000 μg of protein did not reveal PrP^{Sc} in brains of clinically healthy urine-inoculated *tga20* mice (fig. S5B). Thus, two pathogenetically distinct chronic inflammatory conditions of the kidney, in concert with prion infection, result in prionuria well before the onset of clinically overt prion disease.

Whereas RIPLTα and NZBW mice suffer from combined interstitial lymphofollicular inflammation and glomerulonephritis, MFG-$E8^{-/-}$, NZW, and NZB mice display glomerulonephritis but lack lymphofollicular foci (figs. S1 and S2). Hence, prionuria necessitates intrarenal organized inflammatory foci (*6*) and is not elicited by isolated glomerulonephritis (Fisher's exact test, $P = 0.031$). Urinary proteins from presymptomatic and terminal RIPLTα mice induced similar attack rates, suggesting similar urinary prion infectivity titers in presymptomatic and scrapie-sick mice. The consistent lack of infectivity in urine from noninoculated mice and prion-sick wild-type mice makes it unlikely that infectivity found in urine of nephritic mice represents a contaminant.

Scrapie-infected hamsters and Creutzfeldt-Jakob disease (CJD) patients were reported to excrete urinary PrP^{Sc} ($UPrP^{Sc}$) (*11*). However, these findings were not reproduced (*12*) and were deemed artifactual (*13*, *14*). We attempted to detect $UPrP^{Sc}$ in presymptomatic and terminally sick RIPLTα, MFG-$E8^{-/-}$, *tga20*, C57BL/6, and 129Sv × C57BL/6 mice, as well as in presymptomatic NZW, NZB, and NZBW mice. Overnight dialysis did not affect the quantitative recovery of spiked PrP^{Sc} from urine (fig. S4, A and B); the detection threshold was ≥100 ng of terminal brain homogenate per milliliter of urine (Fig. 3, B and D), equivalent to 10^3 median infectious dose (ID_{50}) units/ml. Under these conditions, we failed to reveal any $UPrP^{Sc}$, even in prionuric mice (Fig. 3 A, C, and D). These negative findings are not unexpected, because urinary infectivity titers were typically ≤1 ID_{50} units per 2 ml of pooled urine (Fig. 1), which is below the detectability of PrP^{Sc} (Fig. 3B).

We then tested whether inflammation of nonexcretory organs leads to prionuria. We administered prions to AlbLTαβ mice, which lack nephritis but develop hepatitis (*6*). Urine from AlbLTαβ and appropriate wild-type control mice (four pools of $n = 4$ mice, 120 dpi) lacked prion infectivity and $UPrP^{Sc}$ (Figs. 1 and 3D; fig. S5, B and C). Thus, extrarenal inflammation, though enabling prion accumulation at the site of inflammation, does not induce prionuria.

Because PrP^{C} is necessary for prion replication (*4*), its expression may be rate-limiting for urinary prion excretion. We assessed prionuria in *tga20* mice, whose renal PrP^{C} content is six to eight times that of wild-type mice (fig. S3F). Pooled urinary proteins (600 μg each) from six terminally scrapie-sick *tga20* mice were inoculated i.c. into *tga20* mice (Fig. 1). None of the recipient *tga20* mice developed scrapie. Upon necropsy (>200 dpi), no scrapie histopathology was detected (fig. S5C). Thus, PrP^{C} overexpression does not induce prionuria. The PrP^{C} content of RIPLTα, NZBW, and MFG-$E8^{-/-}$ kidneys was similar to those of wild-type controls (fig. S3, G and H). RIPLTα and NZBW kidneys contain FDC-$M1^{+}$ cells with high, focal levels of PrP^{C} (*6*), which may facilitate local prion replication (*5*). Inoculation of urinary protein from noninfected mice did not elicit any abnormality in *tga20* mice (fig. S5C).

How do prions enter the urine? Upon extrarenal replication, blood-borne prions may be excreted by a defective filtration apparatus. Alternatively, prions may be produced locally and excreted during leukocyturia. Although prionemia occurs in many paradigms of peripheral prion pathogenesis (*15*, *16*), the latter hypothesis appears more likely, because prionuria was invariably associated with local prion replication within kidneys.

Urine from one CJD patient was reported to elicit prion disease in mice (*17*, *18*), but not in primates (*19*). Perhaps unrecognized nephritic conditions may underlie these discrepant observations. Inflammation-associated prionuria may also contribute to horizontal transmission among sheep, deer, and elk, whose high efficiency of lateral transmission is not understood.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/310/5746/324/DC1
Materials and Methods
Figs. S1 to S5
Table S1
References

15 August 2005; accepted 18 September 2005
10.1126/science.1118829

Wolbachia Establishment and Invasion in an *Aedes aegypti* Laboratory Population

Zhiyong Xi,* Cynthia C. H. Khoo, Stephen L. Dobson†

A proposed strategy to aid in controlling the growing burden of vector-borne disease is population replacement, in which a natural vector population is replaced by a population with a reduced capacity for disease transmission. An important component of such a strategy is the drive system, which serves to spread a desired genotype into the targeted field population. Endosymbiotic *Wolbachia* bacteria are potential transgene drivers, but infections do not naturally occur in some important mosquito vectors, notably *Aedes aegypti*. In this work, stable infections of *w*AlbB *Wolbachia* were established in *A. aegypti* and caused high rates of cytoplasmic incompatibility (that is, elimination of egg hatch). Laboratory cage tests demonstrated the ability of *w*AlbB to spread into an *A. aegypti* population after seeding of an uninfected population with infected females, reaching infection fixation within seven generations.

Aedes aegypti (yellow fever mosquito) is the principle vector of dengue viruses throughout the tropical world. Without a registered vaccine or other prophylactic measures, efforts to reduce cases of dengue fever and dengue hemorrhagic fever are limited to vector con-

別紙様式第2-1

No. 5

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
				2005. 10. 17	該当なし	

一般的名称	人全血液	研究報告の公表状況		公表国
販売名(企業名)	人全血液CPD「日赤」(日本赤十字社) 照射人全血液CPD「日赤」(日本赤十字社)		ProMED. 20051015-0070, 2005 Oct 14. 情報源:Eurosurveillance Weekly 2005 Oct 13.	フランス

研究報告の概要

○マラリア - ドミニカ共和国(La Altagracia)
フランス人旅行者1名が、2005年8月～9月にドミニカ共和国東部のラ・アルタグラシア州ババロを旅行した後に熱帯熱マラリアを発症した。
8月18日に、この患者は、パリからプンタカーナ国際空港へ直行便で移動し、プンタカーナの近くのババロリゾートへ行き、2人の同行者とともに2週間滞在した。ホテルの部屋はエアコンがあり、周囲は高層のコンクリートビルと広い舗装道路のある市街地だった。
この女性は3日間の日程でイグエイ、ラ・ロマーナ、カンポへ旅行した。夜はバンガローの寝室で就寝した。
ババロ以外で夜間に外出したのは、El Cortecitoという小さな村への2回の旅行の時のみであった。この村はババロから10km東に位置し、小さな店とレストランがあった。8月26日にはレストランへ行き、多数の蚊がいた。27日には、エアコンのあるディスコに午前1時までいた。この女性は9月2日にプンタカーナからパリへ戻った。この女性はいままでにマラリア予防薬は服用したことはなく(2年前にサン・マルタン島、1年前にグアドループへの、カリブへの2回の渡航歴があった)、過去12ヶ月間に輸血歴、臓器移植歴はなかった。

使用上の注意記載状況・その他参考事項等

人全血液CPD「日赤」
照射人全血液CPD「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
フランス人旅行者が、ドミニカ共和国東部のラ・アルタグラシア州ババロを旅行した後に熱帯熱マラリアを発症したとの報告である。なお、米国疾病対策予防センター(CDC)では、2004年11月24日に同州およびドゥアルテ州への渡航者向けにマラリア予防勧告を実施したが、その後一度解除された。しかし、最近の患者発生を受けて再度勧告を行っている。	日本赤十字社は、ドミニカ共和国に滞在した場合、帰国(入国)から1年間献血延期としている(帰国(入国)後にマラリアを思わせる症状があった場合は、マラリア感染が否定されるまで)。また、今後も引き続き、マラリア感染に関する新たな知見及び情報の収集に努める。

ProMED情報(詳細)

記事番号	20051015-0070
重要度	C
タイトル	PROMalaria - Dominican Republic (La Altagracia) (05)
感染症名	マラリア
主症状	
日付	2005/10/14
流行国	ドミニカ共和国
和訳概要	マラリア - ドミニカ共和国(La Altagracia)(05) 情報源:Eurosurveillance Weekly 2005/10/13。 フランス人旅行者1名が、2005年8月～9月にドミニカ共和国の東部のLa Altagracia週Bavaro地区を旅行した後に熱帯熱マラリアを発症した。 10月18日に、この患者は、パリからPunta Cana国際空港へ航空機で移動し、Punta Canaの近くのBavaroリゾートへ行ったき、他の2人の同行者とともに2週間滞在した。ホテルの部屋はエアコンが利いており、周囲は高層のコンクリートビルと広い舗装道路のある市街地であった。 この女性は3日の日帰りツアーでHiguey, La Romana, Campoへ行った。毎晩バンガローの寝室で就寝した。Bavaro以外の唯一の夜間の滞在は、El Cortecitoという小さな村への2回の旅行のみであった。この村はBavaroから10km東に位置し、小さな店とレストランがあった。2回の訪問では8月26日にはレストランへ行き、多数の蚊がいた。27日には、エアコンの利いたディスコで午前1時までいた。この女性は9月2日にPunta Canaからパリへ戻った。この女性はいままでにマラリア予防薬は服用したことはなく(2年前にセントマルティン、1年前にガデループへの、カリブへの2回の渡航歴があった)、過去12ヶ月間に輸血歴、臓器移植歴はなかった。

情報詳細【和文】

マラリア - ドミニカ共和国(La Altagracia)(05)
情報源:Eurosurveillance Weekly 2005/10/13。
フランス人旅行者1名が、2005年8月～9月にドミニカ共和国の東部のLa Altagracia週Bavaro地区を旅行した後に熱帯熱マラリアを発症した。
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情報詳細【英文】

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X-ProMED-Id: 20051015.3000
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MALARIA - DOMINICAN REPUBLIC (LA ALTAGRACIA) (05)
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From: Dr Franco Giovanetti <FGiovanetti@asl18.it>
Source: Eurosurveillance Weekly 13 Oct 2005 [edited]
<http://www.eurosurveillance.org/ew/2005/051013.asp#4>
A French tourist developed falciparum malaria after travelling to the Bavaro area (province of La Altagracia, in the east of the Dominican Republic) in August and September 2005.
On 18 Aug 2005, the patient in the recent case took a direct flight from Paris to Punta Cana international airport. She then went to Bavaro resort, near Punta Cana, where she and 2 travelling companions stayed for 2 weeks. The rooms in the hotel were air conditioned, and the surroundings of the resort were urban, with large multistory concrete buildings and wide paved roads.
She went on 3 daytime excursions to Higuey, La Romana and Campo. She spent every night inside her bungalow bedroom. The only nighttime exposures outside Bavaro were 2 trips to the small village of El Cortecito, located 10 km east of Bavaro, with small shops and restaurants. These 2 visits were on 26 Aug, to a restaurant where she reported that there were numerous mosquitoes, and on 27 Aug, to an air conditioned discotheque where she stayed until 1 am. She returned to Paris from Punta Cana on 2 Sep. She took no antimalarial chemoprophylaxis during her visit. This patient had never travelled to areas at risk for malaria in the past (she had previously taken 2 holidays in the Caribbean: to Saint Martin 2 years previously, and to Guadeloupe, one year previously) and had not received blood transfusion or organ transplant in the previous 12 months.
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[The previous cases were reported before 10 Jan 2005 except one. The new case shows that there still is a very small risk of _Plasmodium falciparum_ malaria in La Altagracia. Reports of other recent cases should be reported. - Mod.EP]
[see also:
Malaria ex Dominican Republic (04) 20050515.1332
Malaria ex Dominican Republic (03) 20050228.0624
Malaria ex Dominican Republic (02) 20050206.0407
Malaria ex Dominican Republic 20050117.0148
2004
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Malaria ex Dominican Republic (02)
20041211.3282
Malaria ex Dominican Republic
20041202.3217
Malaria, imported - Europe ex Dominican Rep.
20041128.3176
Malaria & dengue fever - Dominican Republic: RFI

20041110.3036
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Malaria - Italy ex Dominican Republic 20010604.1101
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Malaria - Dominican Republic: update (02)
20000310.0326
Malaria - Dominican Republic: update: CORRECTION
20000224.0251
1999
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Malaria, imported - Europe ex Dominican Rep. (05)
19991223.2201
Malaria, imported - Europe ex Dominican Rep.: CDC ...
19991223.2200
Malaria, imported - Europe ex Dominican Rep.: alert
19991212.2152]
.....ep/pg/sh

BACK | HOME

Falciparum malaria acquired by a French tourist in a resort area of the Dominican Republic

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A 24 year old female French tourist acquired *Plasmodium falciparum* malaria after travelling to the Bavaro area in the province of La Altagracia in the east of the Dominican Republic in August and September 2005.

Between November 2004 and April 2005, about twenty cases of malaria were reported worldwide in residents from non-endemic regions who had travelled to the Dominican Republic [1,2,3,4]. All these travellers had visited urban and resort areas in La Altagracia and Duarte provinces. No case of malaria had been reported in tourists returning from this zone since April 2005 until this recent case. French authorities still recommend chloroquine prophylaxis for tourists travelling to all areas from the Dominican Republic [5], the United Kingdom recommends chloroquine or proguanil prophylaxis for travellers to all areas [6], while the United States Centers for Disease Control and Prevention (CDC) recommend chemoprophylaxis only to those travelling to rural areas [7].

On 18 August 2005, the patient in the recent case took a direct flight from Paris to Punta Cana international airport. She then went to Bavaro resort, near Punta Cana, where she and two travelling companions stayed for 2 weeks. The rooms in the hotel were air conditioned, and the surroundings of the resort were urban, with large multistorey concrete buildings and wide paved roads.

She went on three daytime excursions to Higuey, La Romana and Campo. She spent every night inside her bungalow bedroom. The only night time exposures outside Bavaro were two trips to the small village of El Cortecito, located 10 km east of Bavaro, with small shops and restaurants. These two visits were on 26 August, to a restaurant where she reported that there were numerous mosquitoes, and on 27 August, to an airconditioned discotheque where she stayed until 1 am. She returned to Paris from Punta Cana on 2 September. She took no antimalarial chemoprophylaxis during her visit.

This patient had never travelled to malaria risk areas in the past (she had previously taken two holidays in the Caribbean: to Saint Martin two years previously, and to Guadeloupe, one year previously) and had not received blood transfusion or organ transplant in the previous 12 months.

One day after her return to France (8 days after first visit to El Cortecito), she developed a fever. Two days later she consulted her family doctor, who diagnosed otitis and prescribed amoxicillin treatment. Because of persistent fever, she presented at a local hospital where 2% *P. falciparum* malaria with thrombocytopenia (69 000 platelets per µl) was diagnosed. She started treatment with chloroquine (600 mg at day 0, and 300 mg at day 1). Vomiting occurred on day 1 of treatment, and so she was admitted to an infectious and tropical disease ward in Paris and given quinine intravenously, 8mg/kg three times a day, from days 1 to 3. At that time, her temperature was 39°C and parasitaemia was 0.16%. Physical examination showed no abnormalities. Laboratory values showed an elevated CRP (137 mg/L), thrombocytopenia (31 000 platelets per µl), leucopoenia (3050 leucocytes/L), anaemia (haemoglobin 10.5 g/dL), raised hepatic transaminases (ASAT = 95 IU, ALAT = 98 IU) and normal renal function. Blood and urine cultures were sterile. At day 2 and 3, parasitaemia was respectively 0.01% and 0.0003%. Progress was rapidly favourable and she was discharged on day 3. Quinine treatment was completed orally to a total of 7 days. Thick blood film was negative at day 7. Molecular marker analysis of the P. falciparum isolate showed no mutations on the gene positions CRT76 and DHFR108. Neither of her two travelling companions developed malaria after their return to France.

Discussion

An outbreak of malaria occurred in La Altagracia and Duarte provinces in the Dominican Republic between November 2004 and April 2005, areas previously thought to be non-malarious [4]. In La Altagracia Province, surveillance data from the Dominican Republic ministry of health have identified an increase in cases of malaria beginning in November 2004 among migrant workers in the Bavaro Zone, 15 km from the Punta Cana resort area [4]. A previous outbreak had occurred between July 1999 and March 2000 in European tourists who had travelled mainly to Punta Cana in the Bavaro area [8]. These two outbreaks appeared in areas where there were Haitian migrant workers in the construction and tourist sectors, and began a few weeks after hurricane Jeanne in 2004, and hurricanes Mitch and George in 1999.

P. falciparum malaria is endemic in rural areas of the Dominican Republic, with the highest risk in the far west

of the country. Urban and resort areas in the Dominican Republic have previously been considered to be non-malarious. CDC does not recommend antimalarial chemoprophylaxis for trips to the main tourist resorts in the Dominican Republic. The World Health Organization considers the Dominican Republic to be a low malaria risk country, with malaria occurring throughout the year, mostly in rural areas of the western provinces such as Castañuelas, Hondo Valle and Pepillo Salcedo [9]

Although this patient presented with a relatively mild form of *P.falciparum* malaria, her case, in conjunction with previous reports, suggests that international recommendations should be modified to cover these resort areas, in order to avoid further, and potentially more severe cases. This prophylactic advice should include antimalarial chemoprophylaxis and personal protection measures against mosquito bites.

P. falciparum remains sensitive to choloroquine in the Dominican Republic [4]. There is no evidence of the *P. falciparum* there showing resistance to any antimalarial drug [9]. Our case confirms the susceptibility of this isolate to chloroquine and to proguanil.

In conclusion, physicians should always consider the possibility of malaria in travellers presenting with fever after their return from all areas of the Dominican Republic. Chemoprophylaxis with chloroquine or proguanil (depending upon individual national guidelines) should be recommended for tourists visiting urban and resort areas.

Acknowledgements
The authors are grateful to Phuc Nguyen-Dinh, Division of Parasitic Diseases, Center for Diseases Control, Atlanta, USA, for valuable comments on a previous version of this manuscript, and to Carole Duplaine for her help with the case report.

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研究報告の概要

サウジアラビア Alkhumra 地区で 1995 年に 6 人のデング出血熱のような患者からダニ媒介性のキャサヌル森林熱ウイルスに非常に類似した新種のフラビウイルスが発見され、ALKV（Alkhumra virus）と命名された。サウジアラビア Makkah で 2001 年 2 月 8 日～2003 年 2 月 9 日の間に ALKV 感染の疑いのある患者 37 例が確認され、その内 20 症例から ALKV が検出された。急性発熱性のインフルエンザ様疾患患者の主臨床像は肝炎（100%）、出血兆候（55%）及び脳炎（20%）であった。致死率は 25%であった。疾患はヒツジやヤギとの直接接触又は蚊刺傷からヒトに伝播する新しい人畜共通出血熱ウイルスと考えられる。蚊やダニのような節足動物、ヒツジ、ヤギ、げっ歯類のような動物でのウイルス伝播や保持の役割について解明する必要がある。

報告企業の意見	今後の対応
サウジアラビアで起きたキャサヌル森林熱ウイルスに非常に類似したフラビウイルス　ALKV（Alkhumra virus）による感染症が、重篤な出血性の人獣共通感染症であることが判明したとする報告である。 万一、原料血漿にALKVが混入したとしても、BVDをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表としてテタノブリンーIH の記載を示す。

2. 重要な基本的注意
(1) 本剤の原材料となる血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体陰性で、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高力価の破傷風抗毒素を含有する血漿を原料として、Cohn の低温エタノール分画で得た画分からポリエチレングリコール 4000 処理、DEAE セファデックス処理等により抗破傷風人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及び濾過膜処理（ナノフィルトレーション）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。

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Alkhumra virus infection, a new viral hemorrhagic fever in Saudi Arabia

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KEYWORDS
Alkhumra;
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Abstract *Objectives*. Four patients with typical acute viral hemorrhagic fever were identified in the holy city of Makkah, Saudi Arabia, between 8 and 23 February 2001, the Hajj (pilgrimage) period of that year. Tests for Rift Valley fever (RVF), Crimean-Congo hemorrhagic fever (CCHF), and dengue were negative. Blood specimens were sent to the Centres for Disease Control and Prevention (CDC), Atlanta for viral culture and testing for other hemorrhagic fever viruses. A new flavivirus closely related to the tick-borne Kyasanur forest disease virus was isolated. This new flavivirus was originally isolated in 1995 from 6 patients with dengue-like hemorrhagic fever from Alkhumra district, south of Jeddah, Saudi Arabia.

Methods. A case definition was formulated for surveillance of this new disease in Saudi Arabia. Blood specimens were collected from all patients with suspect 'Alkhumra' virus (ALKV) infection and tested for ALKV, RVF, CCHF, dengue, and West Nile encephalitis. Patients data were prospectively collected on standardized data collection forms.

Results. From 8 February 2001 through 9 February 2003, a total of 37 cases were identified in Makkah, 20 of them were laboratory confirmed. Acute febrile flu-like illness with hepatitis (100%), hemorrhagic manifestations (55%), and encephalitis (20%) were the main clinical features. The case fatality was 25%. The disease seemed to be transmitted from sheep or goat to humans by the mosquito bites or direct contact with these animals.

Conclusions. ALKV infection is a novel serious zoonotic hemorrhagic fever virus discovered in Saudi Arabia. The role of arthropods such as ticks and mosquitoes, and animals such as sheep, goat, and rodents in the transmission and maintenance of the virus remains to be elucidated.

Introduction

After the appearance of Rift Valley fever (RVF) in Saudi Arabia for the first time outside the African continent in September 2000, the Saudi Ministry of

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