La Rete per le Malattie Infettive: il Modello del Lazio

SEMPLICE INTEGRAZIONE DI SERVIZI
O
OPPORTUNITÀ PER ACCRESCERE QUALITÀ ED EFFICIENZA DEL SISTEMA?

Giovedì 10 Marzo 2011 ore 15.00 – 18.30

Venerdì 11 Marzo 2011 ore 08.30 – 18.00

La diagnostica di laboratorio in tempo reale per casi ad elevata contagiosità

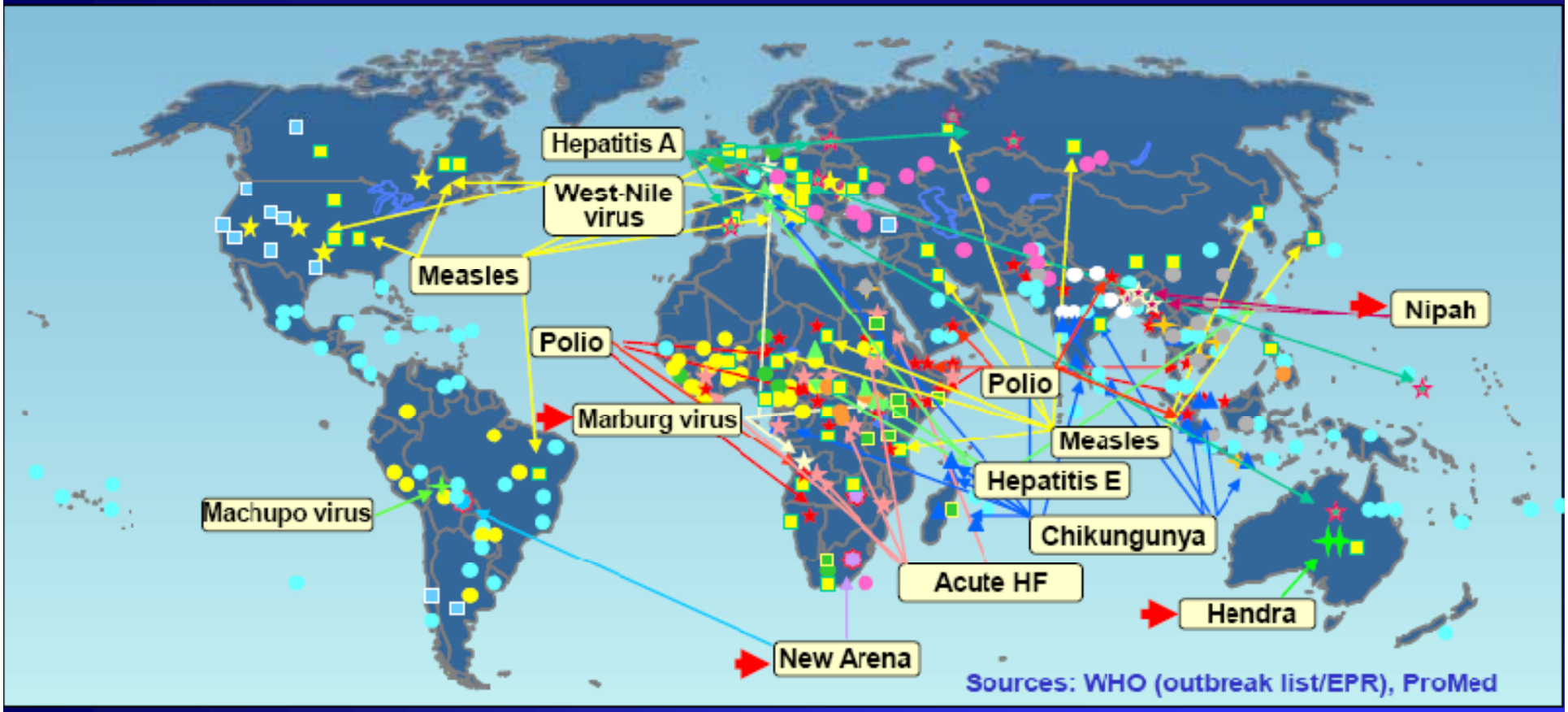
Maria R. Capobianchi
Laboratory of Virology
capobianchi@inmi.it



World Health Organization

WHO Collaborating Center for clinical care, diagnosis, response and training on Highly Infectious Diseases

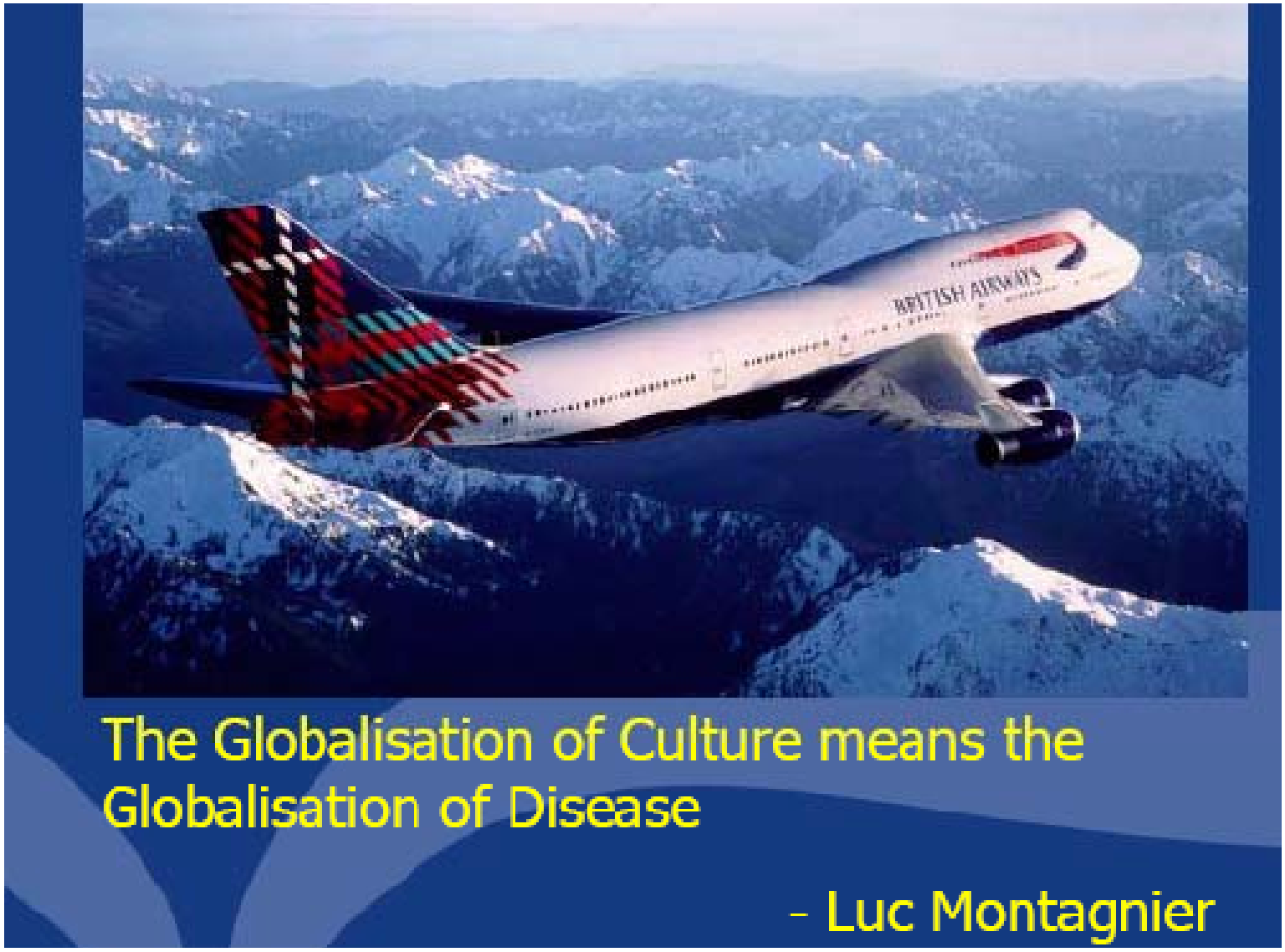
Viral Threats Worldwide
2005 / 2006 / 2007 / 2008 / 2009



- Dengue/dengue haemorrhagic fever
- Ebola / Reston
- Lassa
- Yellow fever
- Influenza
- Crimean Congo haemorrhagic fever
- Japanese Encephalitis
- Viral Meningitis
- Rift Valley fever
- Hanta

ENIVD 04 / 10

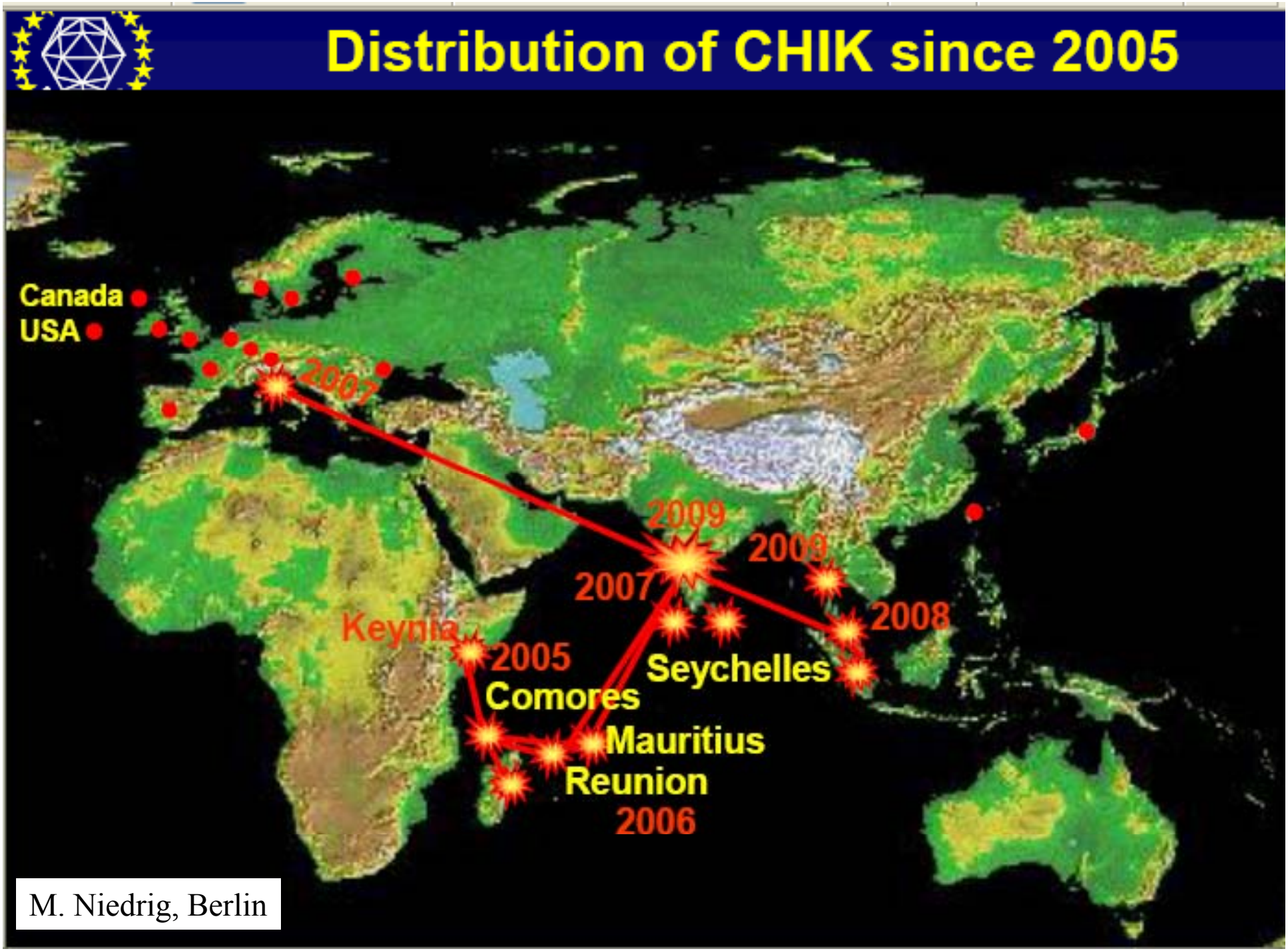
M. Niedrig, Berlin



"***No city on the earth is now more than 24 hours away from any other***". Economist 2003

"***Annually, the world's airlines carry a staggering total approaching some two billion passengers. At any one moment, about half a million people world-wide are flying in commercial aircraft***
".Select Committee on Science and Technology Fifth Report UK Parliament 2000

Distribution of CHIK since 2005





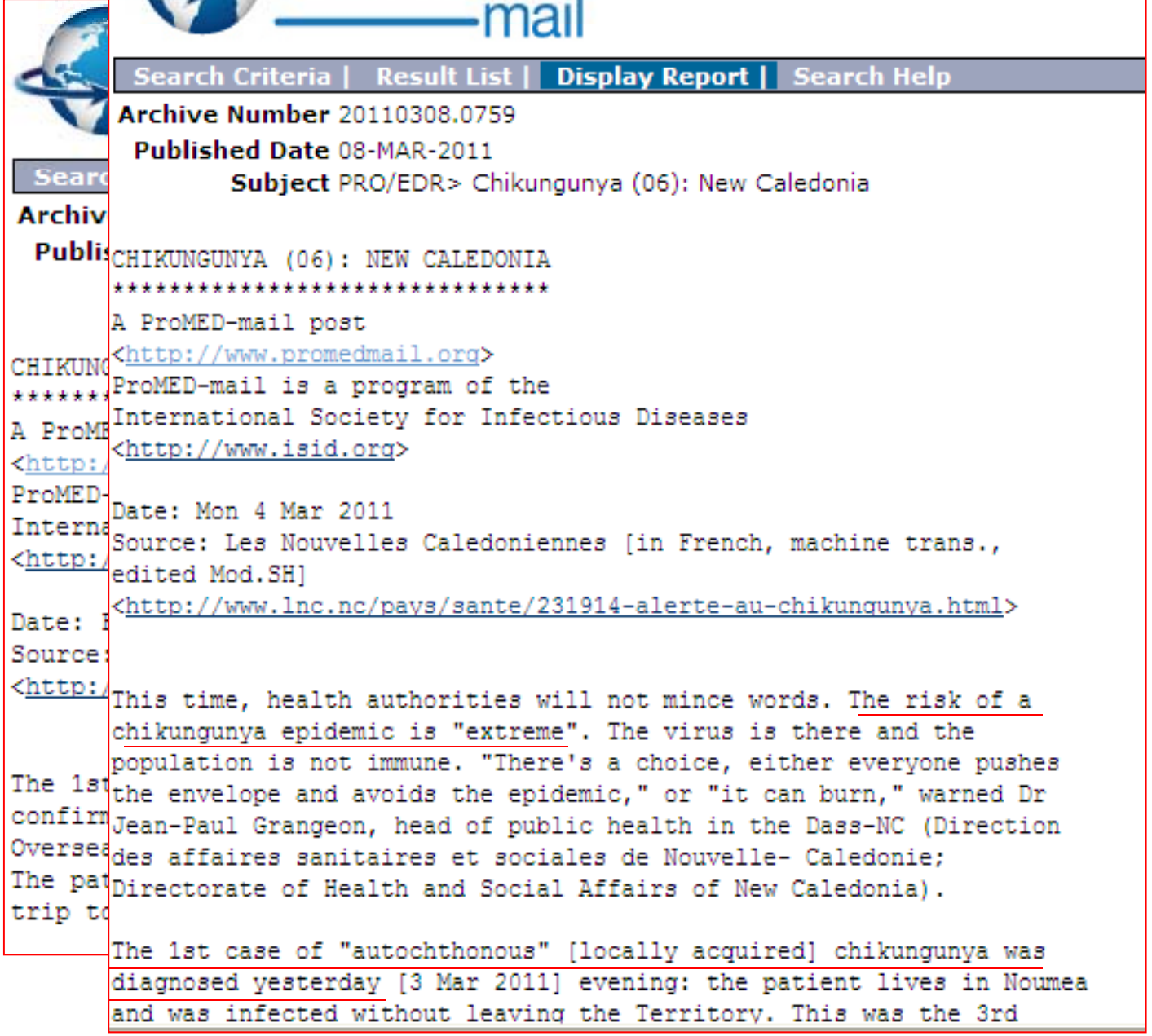
Search Criteria | Result List | Display Report | Search Help

Archive Number 20110226.0631
Published Date 26-FEB-2011
Subject PRO/EDR> Chikungunya (05): New Caledonia ex Indonesia

CHIKUNGUNYA (05): NEW CALEDONIA ex INDONESIA
****
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: Fri 25 Feb 2011
Source: Romandie [in French, trans. LMI, edited]
<http://www.romandie.com/infos/news2/110225103148.m4cw512b.asp>

The 1st ever diagnosed case of chikungunya in New Caledonia was confirmed Friday [25 Feb 2011] by the authorities of the French Overseas Territory. They reported that the patient recovered today. The patient whose age and sex were not disclosed was infected during a trip to Indonesia.



ProMED mail

Search Criteria | Result List | Display Report | Search Help

Archive Number 20110308.0759
Published Date 08-MAR-2011
Subject PRO/EDR> Chikungunya (06): New Caledonia

CHIKUNGUNYA (06): NEW CALEDONIA
****
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: Mon 4 Mar 2011
Source: Les Nouvelles Caledoniennes [in French, machine trans., edited Mod.SH]
<http://www.lnc.nc/pays/sante/231914-alerte-au-chikungunya.html>

This time, health authorities will not mince words. The risk of a chikungunya epidemic is "extreme". The virus is there and the population is not immune. "There's a choice, either everyone pushes the envelope and avoids the epidemic," or "it can burn," warned Dr Jean-Paul Grangeon, head of public health in the Dass-NC (Direction des affaires sanitaires et sociales de Nouvelle- Caledonie; Directorate of Health and Social Affairs of New Caledonia).

The 1st case of "autochthonous" [locally acquired] chikungunya was diagnosed yesterday [3 Mar 2011] evening: the patient lives in Noumea and was infected without leaving the Territory. This was the 3rd

Import of suspected and confirmed Viral HFs and SARS to Europe

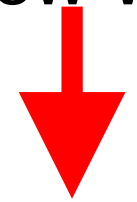
time	Imported from	Imported to	Viral pathogen	N° of cases /fatalities	Business / Tourist
Aug 1999	Ivory Coast	Germany	Yellow Fever	1 / 1	Business
Jan 2000	Ivory Coast	Germany	Lassa	1 / 1	Tourist
Feb 2000	Sierra Leone	U K	Lassa	1 / 1	Business
Mar 2000	Nigeria	Germany	Lassa	1 / 1	Repatriation
Jun 2000	Sierra Leone	Netherlands	Lassa	1 / 1	Business
Dec 2000	Kenya	Germany	Suspected VHF[3]	1 / 1	Tourist
Mar 2001	Sierra Leone	Germany	Suspected VHF[2]	1 / 0	Business
Mar 2001	Chile/Argentine	France	Hanta (Andes)	1 / 0	Tourist
Mar 2001	Sierra Leone	Germany	Suspected VHF[2]	1 / 0	Business
Aug 2001	Bulgaria	Germany	CCHF	1 / 0	Tourist
Sep 2001	Rep. of Chad	France	RVF	2 / 0	Business
Nov 2001	The Gambia	Belgium	Yellow Fever	1 / 1	Tourist
Sep 2002	Nepal	Spain	Suspected VHF[1]	1 / 0	Tourist
Oct 2002	Cameroon	Rep. Ireland	Suspected VHF[2]	1 / 0	Business
Feb 2003	Sierra Leone	U K	Lassa	1 / 1	Business
Feb 2003	China, Vietnam	Europe	SARS	33/1	Tourist/Bus.
2004	USA	Germ./France	West Nile virus	4/0	Tourist
July 2004	Portugal	Rep. Ireland	West Nile virus	2 / 0	Tourist
Oct 2004	Tunesia	France	West Nile Virus	1 / 0	Tourist
Nov 2004	Senegal	France	CCHF	1 / 0	Repatriation
2005 Nov 2006	Reunion India	Europe Lithuania	Chikungunya Rabies	ca. 164/0 1 / 1	Tourist/Bus. Tourist
2007	Morocco	Germany	Rabies	1 / 1	Tourist
Apr 2007	India	Germany	Rabies	1 / 1	Tourist
Jun 2007	India	Italy	Chikungunya	1 / 0	Tourist
Jan 2008	Kenya	Netherlands	Rabies	1 / 1	Tourist
July 2008	Uganda	Netherlands	Marburg	1 / 1	Tourist
Jan 2009	Nigeria	UK	Lassa	1 / 1	Tourist

[1] no final diagnosis, [2] final diagnosis: Malaria, [3] final diagnosis: generalised HSV-1

M. Niedrig, Berlin

Early Detection

The FASTER
We Know What It Is



Rapid Response

The FASTER We Can Take Appropriate Action

Expanded Roles of Infection Control and Microbiology Labs

Infection Control

- Shift toward focused surveillance
  - ICUs
  - devices
  - antimicrobial resistance
- Control strategies are more proactive
  - active intervention
  - control of resistance
  - vaccine strategy
  - outbreak investigation

Microbiology Labs

- Increasingly complex and demanding work
  - increasing resistance
  - (re)emerging pathogens
  - new technology
- Monitoring resistance
- Implementation of molecular epidemiology

Il razionale della diagnosi virologica

Escludere o confermare il più rapidamente possibile una eziologia virale permette di:

- Iniziare precocemente una terapia antivirale specifica
- Eliminare terapie antivirali o antibatteriche empiriche
- Effettuare una valutazione prognostica

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- Individuare e circoscrivere le forme epidemiche

- Evitare il ricorso ad esami costosi non necessari (TAC, emocolture ripetute, esami colturali del CSF, ecc)

- Accorciare il ricovero

October, 2009

Senegalese patient (44ys) residing in Europe,
returned from Senegal to Turin;
after some days he showed fever + signs predictive of coagulation failure.
Susp. viral hemorragic fever (Old World Arenavirus?)

Testing panel included:

- Lassa and other Old World Arena
- Filo
- CCHF
- CHIK, RFV
- Flavi
- HSV, CMV, EBV
- HBV, HCV, HAV, HEV
- Ricketsiae
- Malaria

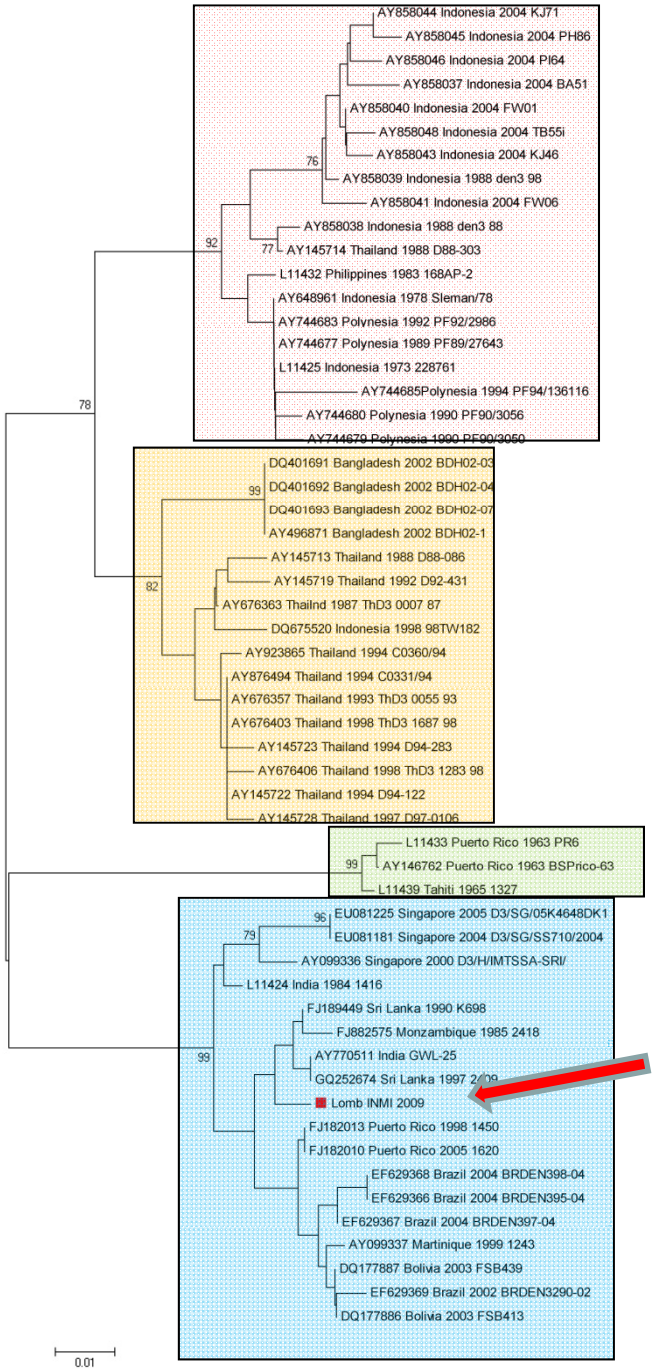
Dengue 3 phylogenetic tree

Genotype I (Southeastern Asia, Philippines and South Pacific islands)

Genotype II (Southeast Asia)

Genotype IV (Puerto Rico, Tahiti)

Genotype III (Asia, east Africa , Americas)



INMI Sample

DEN3 E region 224bp

2143- 2366 of FJ182013 (Puerto Rico 1

S.C. Weaver – Infection, Genetics and Evolution 9 (2009)

Quali sono gli ostacoli nella diagnosi dei patogeni emergenti

- La presentazione clinica iniziale è spesso aspecifica
  - Diagnosi differenziale
- Talvolta l'anamnesi non comprende informazioni su viaggi
- Per la maggior parte degli agenti non esistono metodi commerciali
- Per la maggior parte degli agenti non esistono reagenti e ceppi di riferimento
- La capacità diagnostica è limitata a pochi laboratori
- Possono essere richieste condizioni di elevato biocontenimento
- Il trasferimento di campioni può rappresentare un ostacolo significativo

Nell'ultimo ventennio la tecnologia ha fatto enormi progressi, rendendo disponibili, accanto ai metodi classici (colturali e sierologici) una ampia gamma di metodi molecolari

- End-point PCR
- Real time PCR
- Sequenziamento classico
- Next generation sequencing
- Ibridazione molecolare su microarray

E’ importante disporre dell’intera gamma di possibili approcci diagnostici, perché:

Metodi molecolari:

- Presenza fugace del patogeno, ricerca diretta non efficace
- Necessari primer/probe specifici per i singoli agenti
- Elevata variabilità di alcuni agenti
  - possibilità che il set primer/probe non riconosca le varianti
- Primer/probe meno specifici:
  - rischio di falsi positivi
  - necessità di sequenziamento

Metodi colturali:

- Presenza fugace del patogeno, ricerca diretta non efficace
- Ampio spettro di rilevazione, ma necessità di biocontenimento

Metodi sierologici:

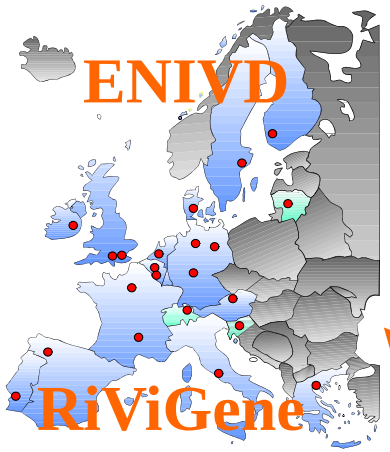
- Reagenti sierologici di riferimento non disponibili
- Cross-reattività verso agenti affini

SARS outbreak in 2003 – lessons learned
Laboratory networking and twinning

La prima epidemia “globalizzata”, è stata affrontata con le armi della globalizzazione:

- Il WHO costituisce un network multicentrico di 13 laboratori per la ricerca sull’eziologia e la diagnostica della SARS
- Il network usa le moderne tecnologie di comunicazione (posta elettronica, siti web protetti) per condividere i risultati in tempo reale
- Si scambiano immagini del virus al microscopio elettronico, sequenze di materiale genetico per l'identificazione del virus e la sua tipizzazione, isolati virali e campioni di vario tipo prelevati da pazienti o durante esami autoptici
- I campioni possono essere analizzati in parallelo in vari laboratori ed i risultati resi noti in tempo reale

Primo esempio di laboratorio globale virtuale



WHO
GOARN-Global
outbreak / alert
response



European
Commission
Research Directory

Public Health
Directory (Sanco)

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

EUROPEAN
EURONET



Networks
with
developing
countries

Global Health Security Action Group

Laboratory Network

Uncertainty in identification and testing



The three factors important in the detection of newly arrived pathogens are:

-diagnosis,

-diagnosis, and

-diagnosis

Rogers DJ & Sanderson V. Foresight. Infectious Diseases: preparing for the future. OSI, London (2006).



Fig. 1. Llamas farmed around Viterbo (Italy)



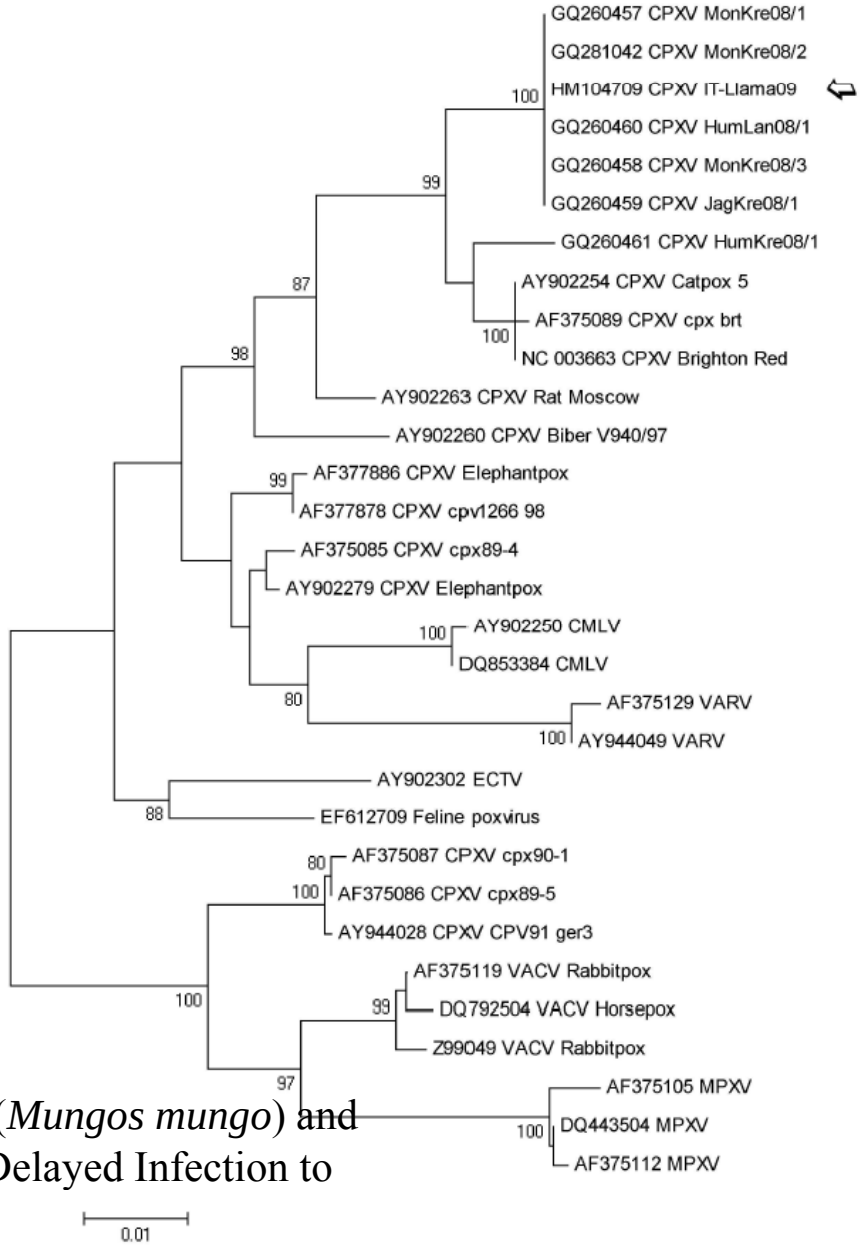


In July 2009, 5 llama adults of 7 present in a farm (Viterbo, Central Italy), exhibited skin lesions at different sites (palpebral conjunctiva, auricles, teats, around the mouth and the anus) evolving from nodules to crusts. None of the other animal species (local and exotic) hosted in the farm developed similar symptoms . No symptoms were declared by the farmers .

Cardeti et al EID, in press

Animal Species	SN Test *Pos/Tot*	IFA Test (IgG) *Pos/Tot*	Serum Titres *(dilution)*
Llama	0/4 (day 19)* 4/4 (day 105)*	/	/ 1:64; 1:11; 1:4; 1:32
Bovine	0/4	/	
Caprine	0/25	/	
Equine	0/3	/	
Asinine	0/18	/	
Human	/	3/4	1:640; 1:20; 1:80

- All the llamas were born in the farm; no contact with exotic animals,
- CPXV strain apparently identical to the German 2008 mongoose isolates (CPXV-MonKre08/1-2-3)
- Virus introduced in the farm through frozen rats, used as food for birds of prey?
- Rats sold from a German distributor throughout Europe (likely fed also to the mangooses from the German oiutbreak)*



Cardeti et al EID, in press

*Kurth A. et al. CPXV Outbreak in Banded Mongooses (*Mungos mungo*) and Jaguarundis (*Herpailurus yagouaroundi*) with a Time-Delayed Infection to Humans. PLoS One 2009

*Schmiedeknecht G. et al. Fatal Cowpox Virus Infection in Captive Banded Mongooses (Mungos mungo). Veterinary Pathology 2010

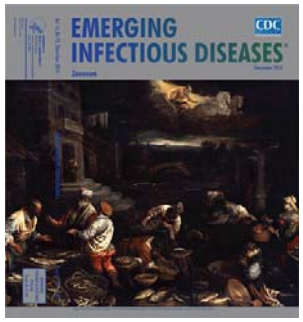
Another recent experience: expect the unexpected!!

The first case: a 64-year-old Italian man spent one week (from April 25th to May 1st, 2010) in South Egypt

Symptoms: During the flight to Italy, he developed high fever, shaking chills, anorexia, malaise, nausea and vomiting, Over the following 5 days the symptoms worsened and he was admitted to hospital (May 10)

Travel history and retrospective reconstruction of possible exposure:
Frequent traveler;
Vaccinated against yellow fever in 1998;
April 29: visit to the camel market of Shalatin;
tick bite on a foot, followed by a small papular lesion and (48 hours after the bite) blurred vision



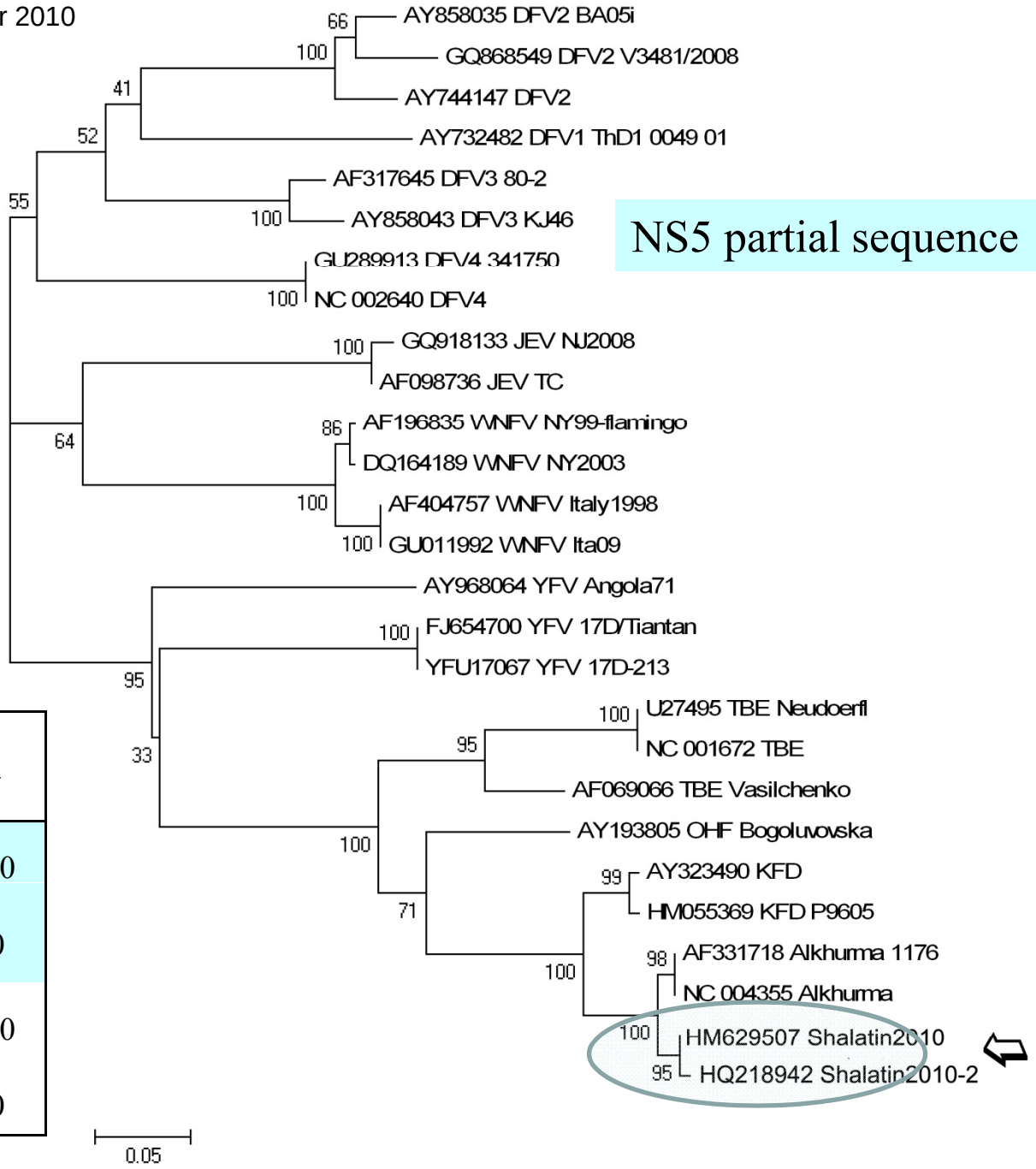


Emerging Infectious Diseases
Vol. 16, No. 12, December 2010

Alkhurma Hemorrhagic Fever in Travelers Returning from Egypt, 2010

Fabrizio Carletti, Concetta Castilletti, Antonino Di Caro, Maria R. Capobianchi, Carla Nisii, Fredy Suter, Marco Rizzi, Alessandra Tebaldi, Antonio Goglio, Cristiana Passerini Tosi, and Giuseppe Ippolito

Collection date	WNV Serology	Dengue Serology
May 10th (Day 12 post exposure)	IgG: ≥1:640 IgM: ≥ 1:20	IgG: ≥ 1:640 IgM: ≥ 1:20
May 27th	IgG: ≥ 1:640 IgM: ≥ 1:20	IgG: ≥ 1:640 IgM: ≥ 1:20



NS5 partial sequence

Uncertainty in identification and testing



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