Historical Significance of Endemic Infectious Diseases and Loss of Warfighter Combat Effectiveness

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Learning Objectives

- Historical review of infectious disease related combat injuries and deaths will be reviewed.
- WWI and the 1918 Influenza Pandemic. SARS, MERS and Wuhan CoV.
- Dengue and US Marine Forces in Saipan during WWII, US Forces in Haiti and Somalia.
- Malaria outbreak in US Marines deployed to Monrovia, Africa.
- Rabies in Afghanistan.
- Leishmaniasis and multi-drug resistant bacteria in US Forces during the Iraq War.
- Lessons learned for future deployments will be discussed.

National Academy of Sciences 2002 Report on "Protecting our Forces"

- Infectious agents remain a substantial threat to the operational capacity of U.S. military forces for three distinct reasons:
- (1) recruits continue to train in groups under crowded conditions, increasing the risk of spread of infectious agents;
- (2) deployed warfighters, whether on combat or peacekeeping missions, continue to come into contact with pathogens with which they have no prior experience and, therefore, against which they have no immunity; and
- (3) warfighters, along with others, face an increasing risk of the intentional use of weaponized infectious agents.

Historical Significance of Infectious Disease Related Combat Injuries

- Alexander the Great just as he was about to achieve world supremacy died in 323 BC at the age of 32 from either typhoid or malaria.
- Napoleon the Great in 1798 halted his Egyptian Campaign when his troops were decimated by an outbreak of plague.
- George Washington in 1777 ordered the mass vaccination of Congressional Soldiers to stop a smallpox outbreak.
- During the Spanish American War of 1898, US Forces invaded Cuba. Fewer than 400 American soldiers were killed in combat during the war. But more than 2,000 contracted yellow fever during the campaign.

History continued

- American combat deaths in World War I totaled 53,402. But 45,000 American Soldiers died of influenza and related pneumonia by the end of 1918.
- During WWII, malaria and dengue were significant causes of soldier illness: 80% of soldiers stationed in Australia and 100% of soldiers in the Solomon Islands became ill from dengue.
- During the Korean War, a new illness was identified, Hantaan Fever with Renal Syndrome causing several 1,000 hospitalization and deaths.
- The Vietnam War resulted in outbreaks of malaria, dengue, typhoid fever, and meliodosis.

History continued

- Conflicts in Haiti and Somalia resulted in large outbreaks of dengue.
- Iraq War resulted in several thousand cases of cutaneous leishmaniasis and an outbreak of multi-drug acinetobacter infections.

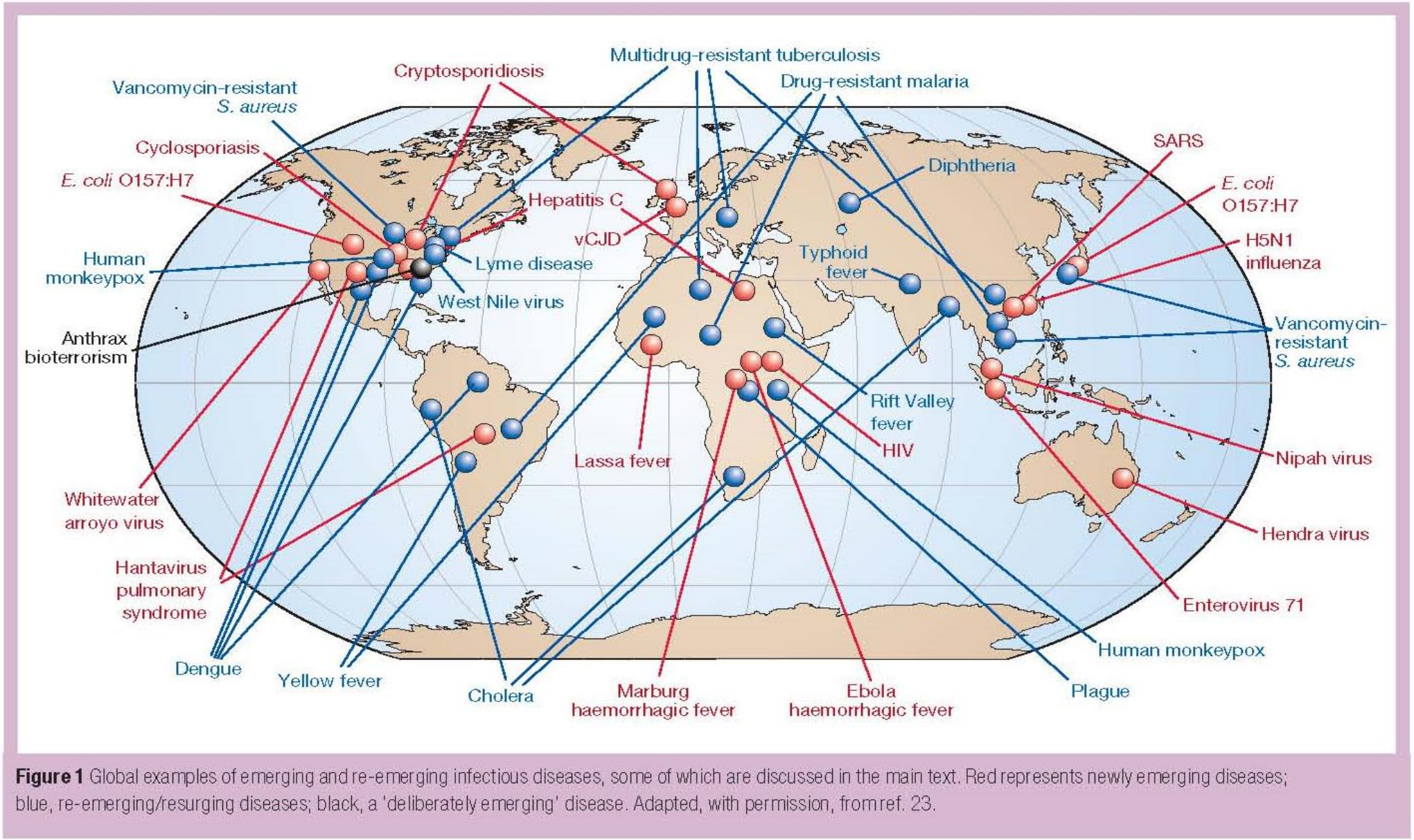


Figure 1 Global examples of emerging and re-emerging infectious diseases, some of which are discussed in the main text. Red represents newly emerging diseases; blue, re-emerging/resurging diseases; black, a 'deliberately emerging' disease. Adapted, with permission, from ref. 23.

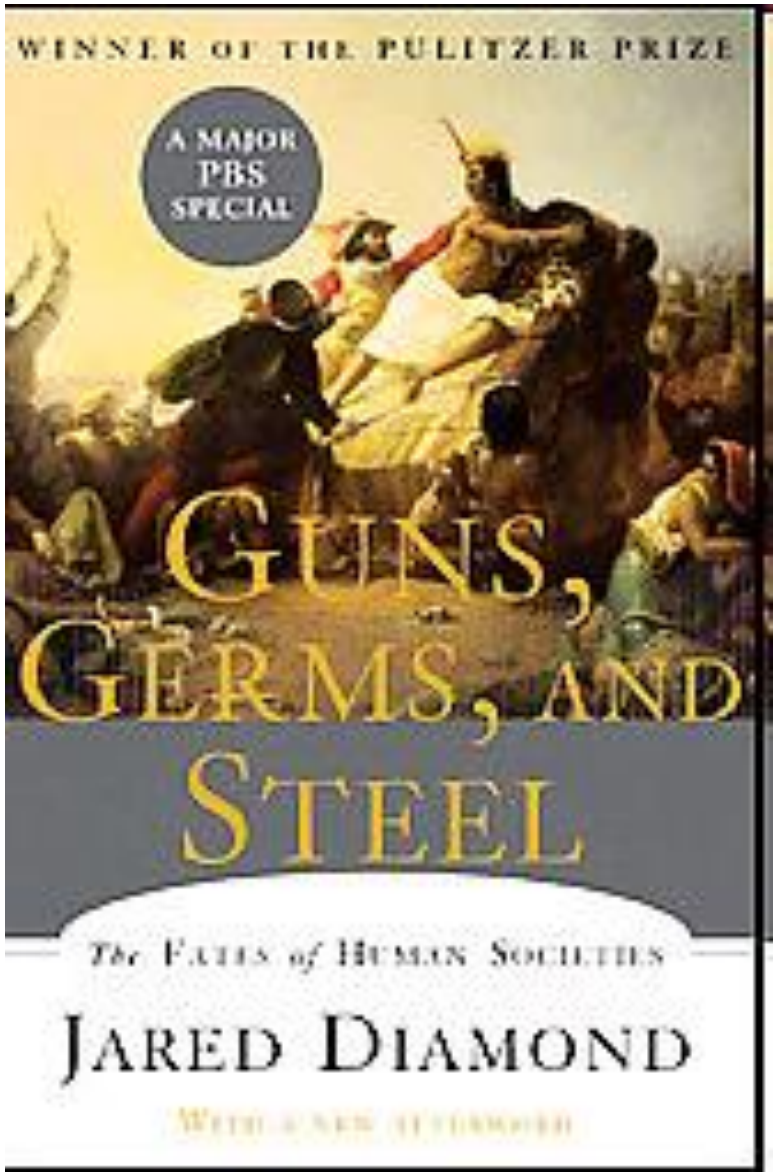
The challenge of emerging and re-emerging infectious diseases. David M. Morens, Gregory K. Folkers & Anthony S. Fauci, Nature, 2004;430, 242-49.

Box 1

Factors involved in the emergence of infectious diseases

Selected factors contribute to the emergence/re-emergence of infectious diseases[25,26]. These factors, which frequently differ for 'newly emerging', 're-emerging/resurging' and 'deliberately emerging' diseases, include genetic, biological, and social, political and economic factors.

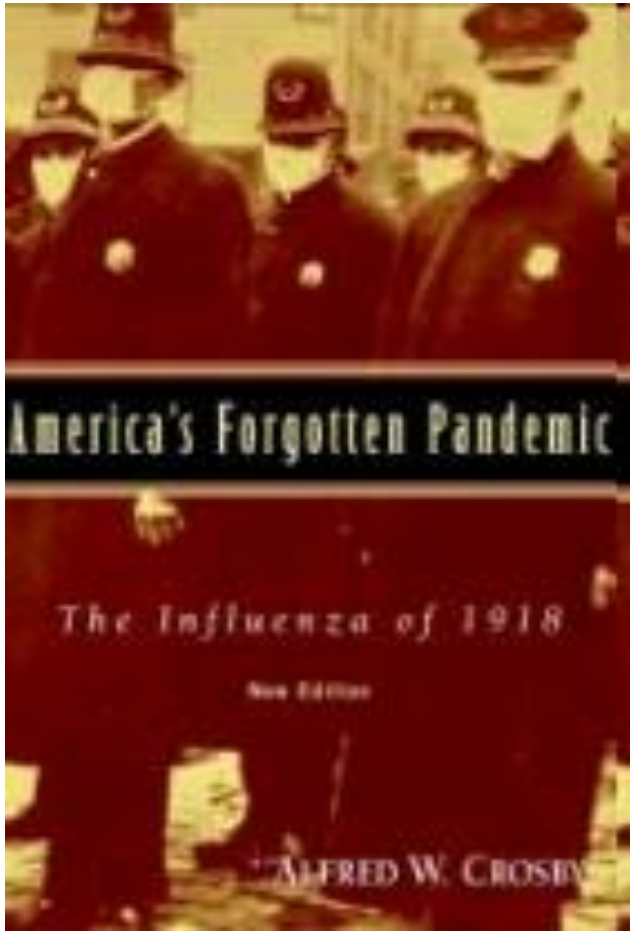
- Microbial adaptation and change
- Human susceptibility to infection
- Climate and weather
- Changing ecosystems
- Human demographics and behaviour
- Economic development and land use
- International travel and commerce
- Technology and industry
- Breakdown of public health measures
- Poverty and social inequality
- War and famine
- Lack of political will
- Intent to harm



"Among animals too, epidemic diseases require dense populations, and they're mainly confined to social animals that provide the necessary large populations. Hence when we domesticated social animals such as cows and pigs, they were already afflicted by epidemic diseases just waiting to be transferred to us".

World War I

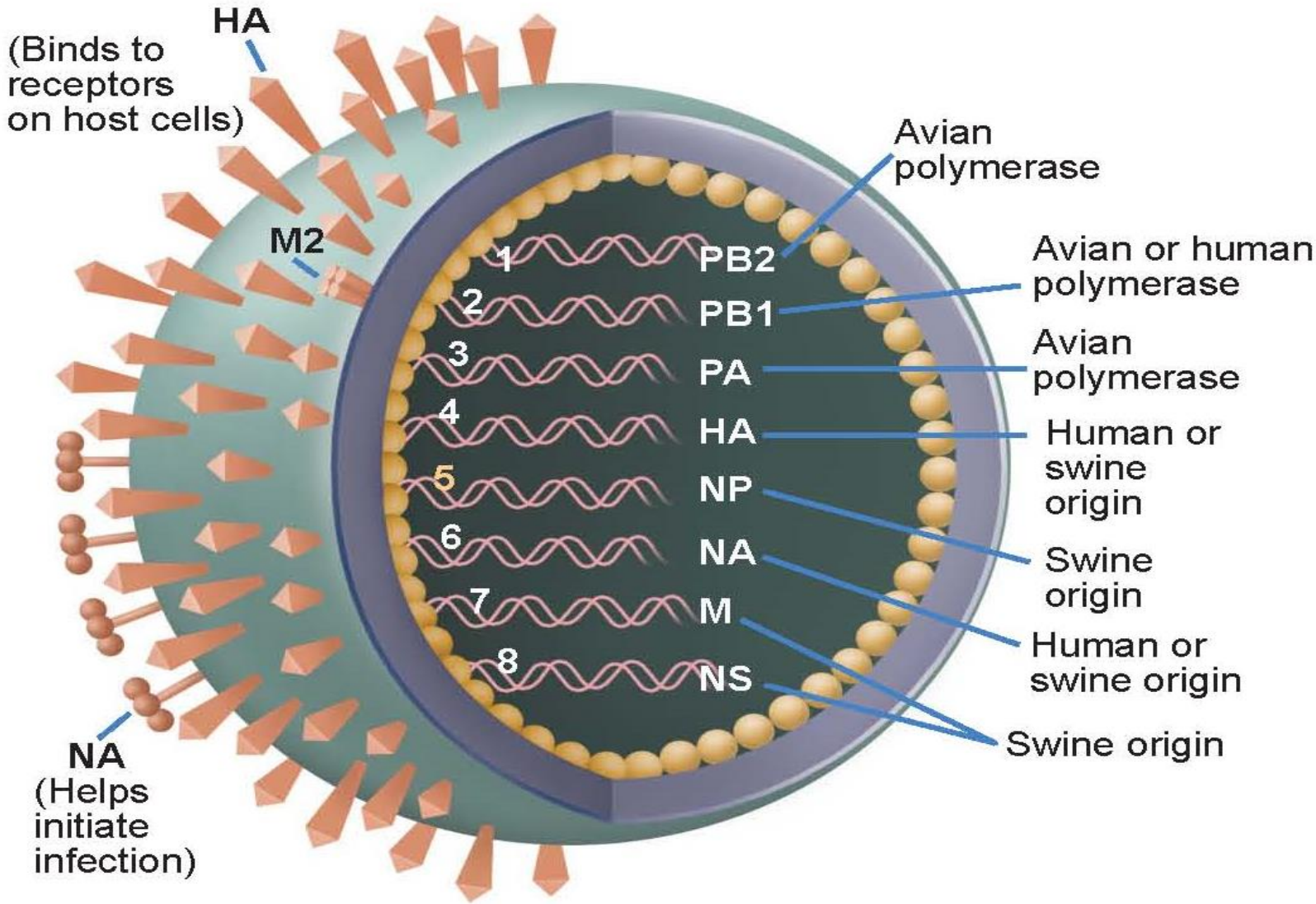
The Forgotten Pandemic: Influenza of 1918



- In 1918 the world was involved in its first global world war. The United States was training and sending over a million soldiers to fight in France.
- Camp Devens was the training ground of the 12th Infantry Division and consisted of 45,000 men training in an encampment build for 35,000.

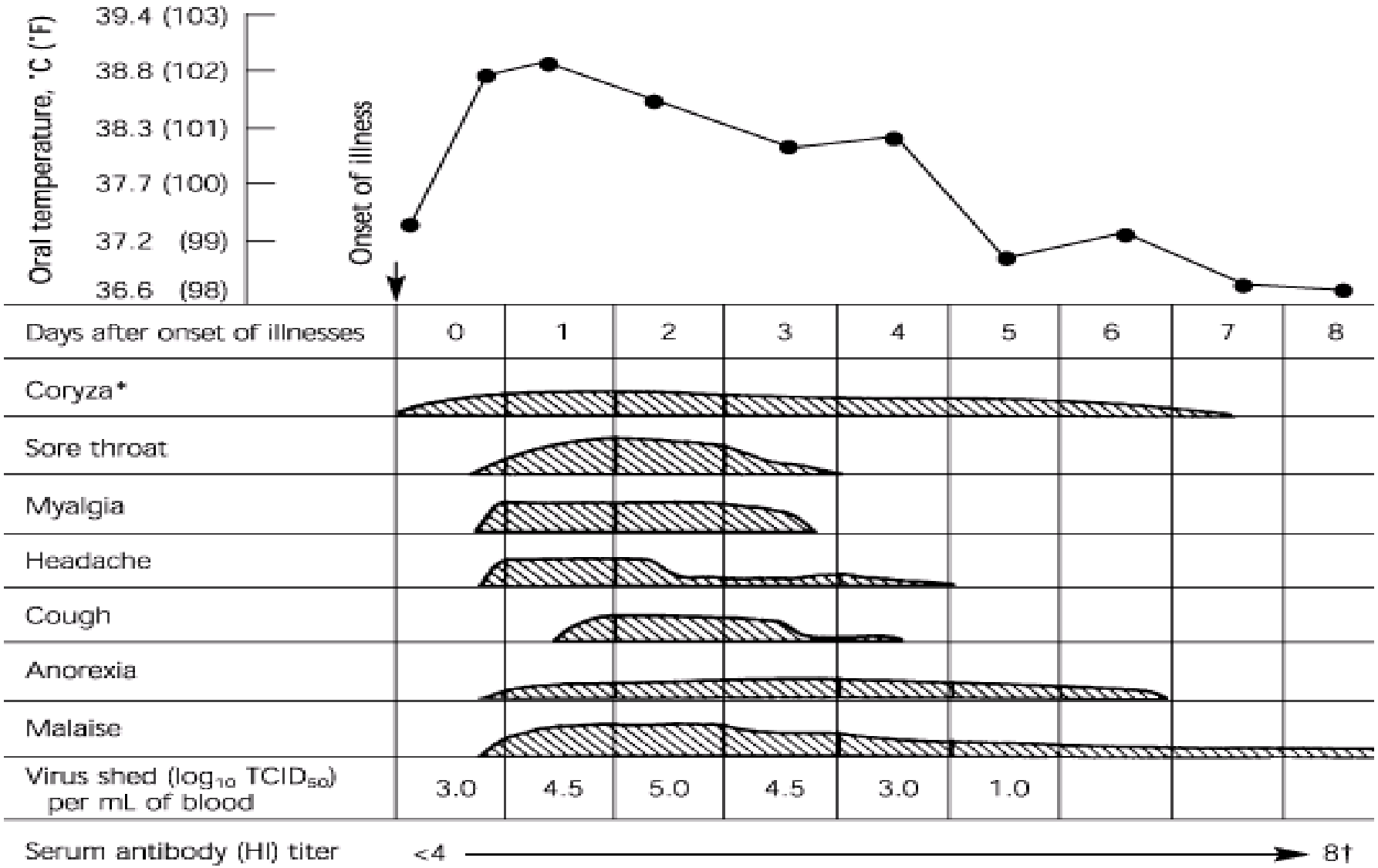
Teaching Points

- Influenza is a Zoonosis: aquatic birds are the source for all genes of influenza.
- Human epidemic influenza is caused by type A and B viruses, both undergo antigenic change in their surface antigens.
- Epidemics are the consequence of antigenic changes- “antigenic drift”.
- Pandemic influenza occurs at unpredictable intervals, result of a major antigenic- “antigenic shift”, only in influenza A.
- Antigenic shift is the evolution of a new human influenza A virus by acquiring a new hemagglutinin gene encoding a different subtype.
- Two subtypes of avian influenza, H5 and H7, can cause severe infections into domestic poultry. Avian influenza viruses do not readily infect humans. In the past 3 years, more than 250 cases of H5N1 infection of humans have occurred, with a mortality of 60%.



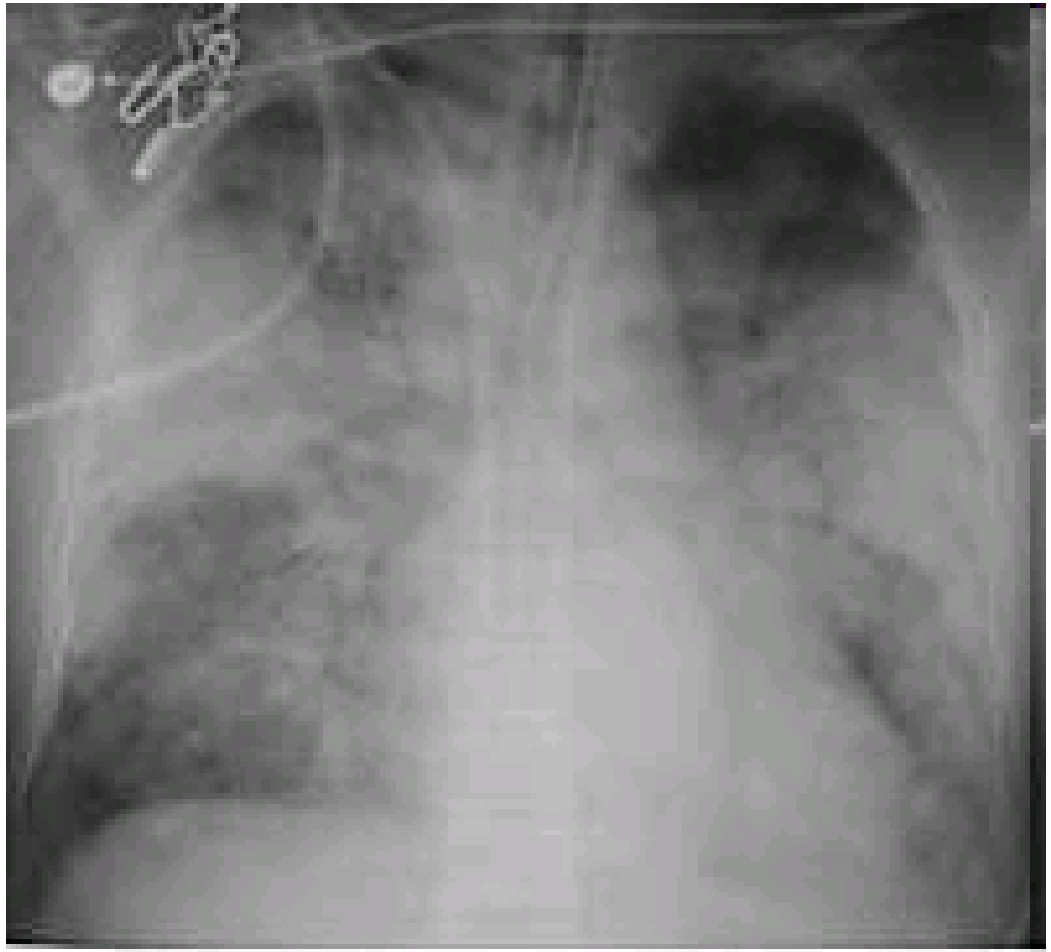
New flus. The influenza viruses now found in North American pigs have genes from both human and bird viruses.

Natural Course of Influenza



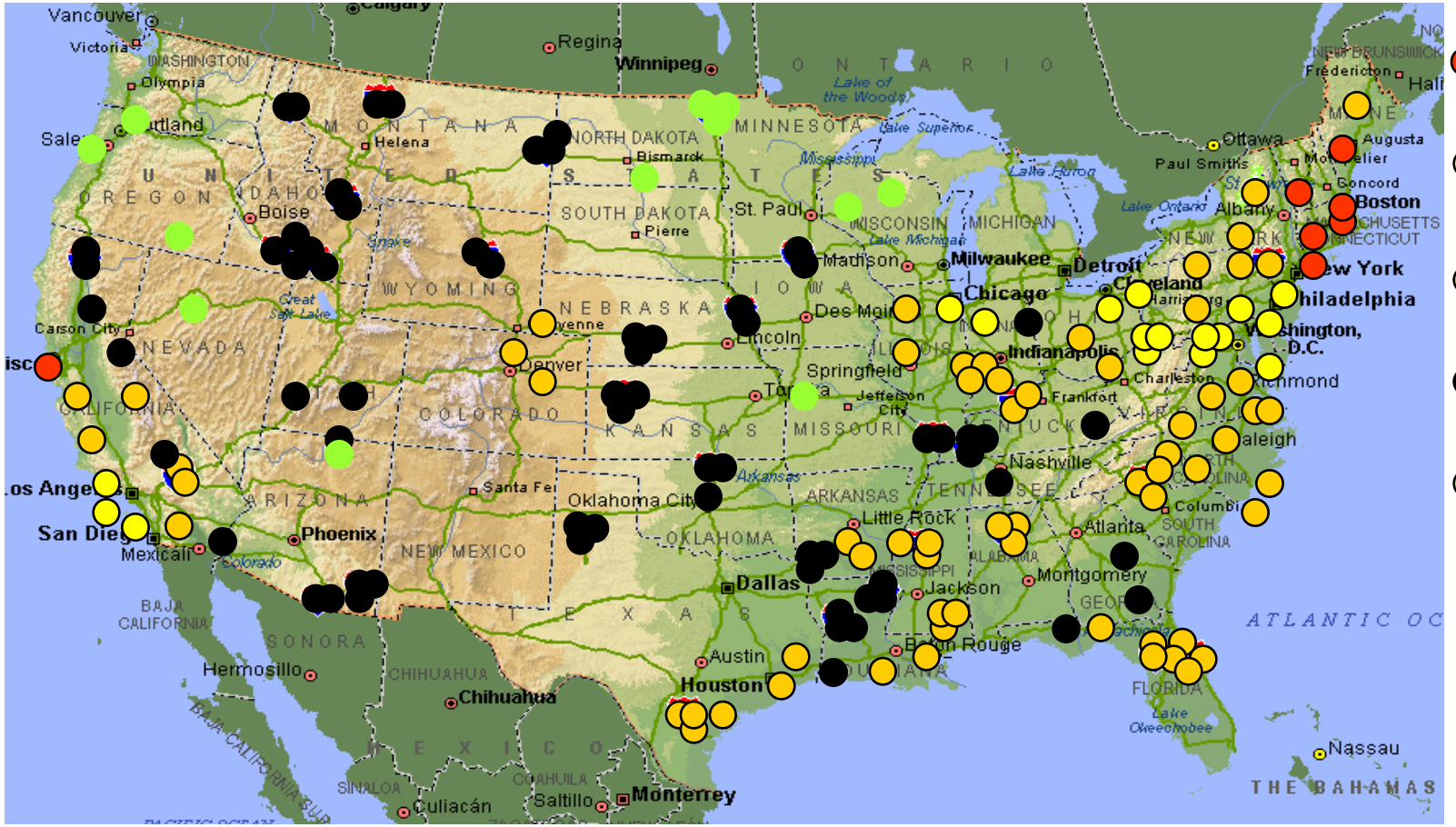
*—*Coryza is an acute inflammatory condition of the nasal mucous membranes with a profuse discharge from the nose.*

†—*Serum antibody titer was 64 at day 21.*



Camp Devens 1918

Spread of Influenza in the United States: 1918



Reported Cases

- Before Sept. 14
- Sept. 14 to Sept. 21
- Sept. 21 to Sept. 28
- Sept. 28 to Oct. 5
- After Oct. 5

Influenza in the Allied Expeditionary Force: France 1918

	Influenza Admission	Pneumonia Admissions	Deaths	Mortality %
Americans				
September	37,935	3,560	2,500	6.0
October	38,655	7,008	5,092	11.2
November	22,066	2,621	1,552	6.3
British				
October	14,000	0	316	2.3
November	48,683	0	3,340	6.9
French				
September	24,280	0	2,195	9.1
October	75,719	0	5,917	7.8
November	32,508	0	2,046	6.3

Summary

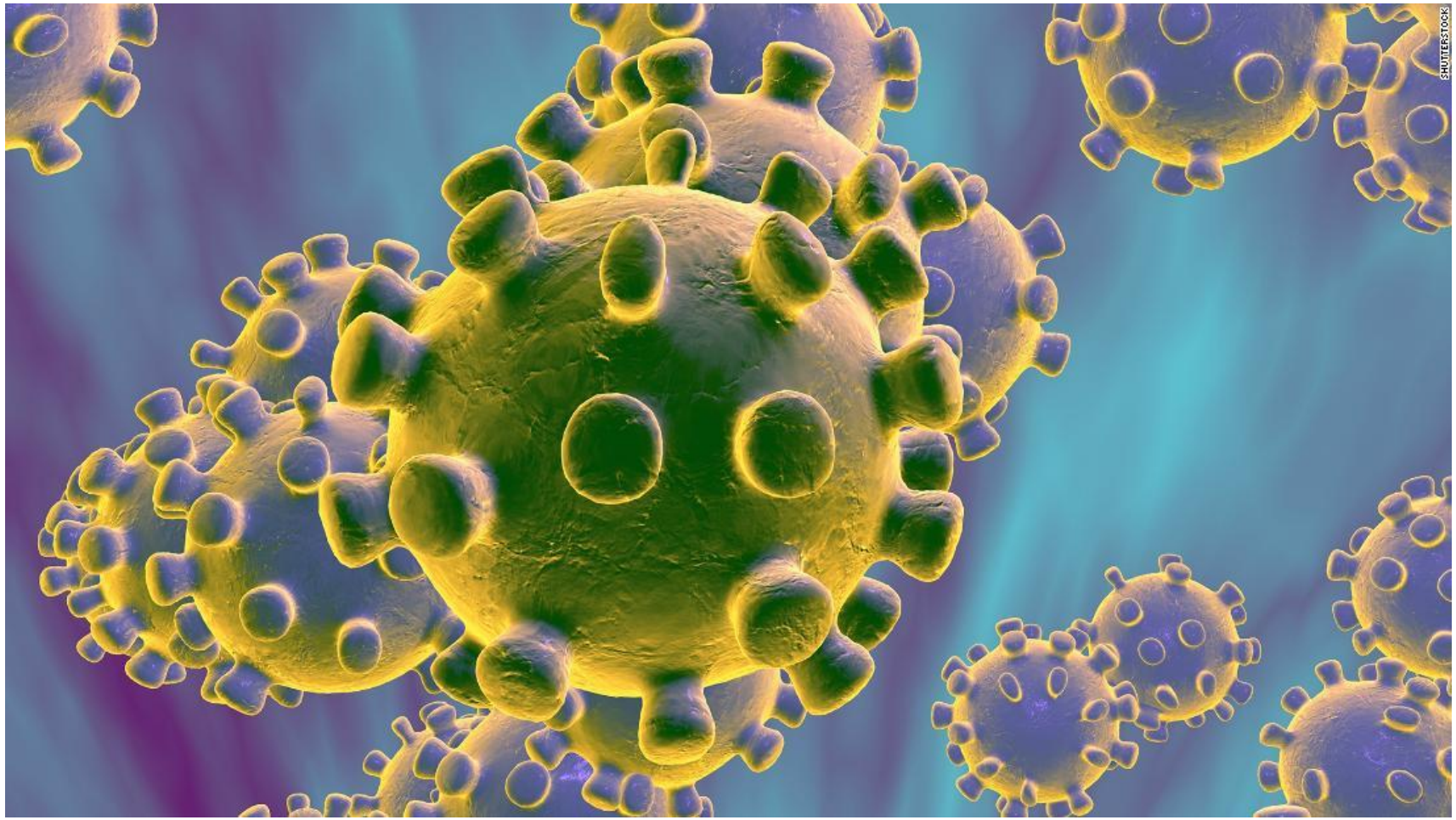
- Influenza A is a zoonosis with a primary reservoir in birds.
- Constant evolution of influenza virus through antigenic shift, drift, reassortment and adaptation through a cycle of birds, swine and humans.
- Future pandemics of influenza A is a certainty.
- Troop overcrowding, poor sanitation, and stress of war contributed to the large outbreak.

Protecting Soldiers

- Minimize overcrowding.
- Influenza vaccine.
- Prompt reporting and isolation from troop barracks.

Emerging Respiratory Threats to the Warfighter

Coronaviruses (CoV)



Severe Acute Respiratory Syndrome (SARS)

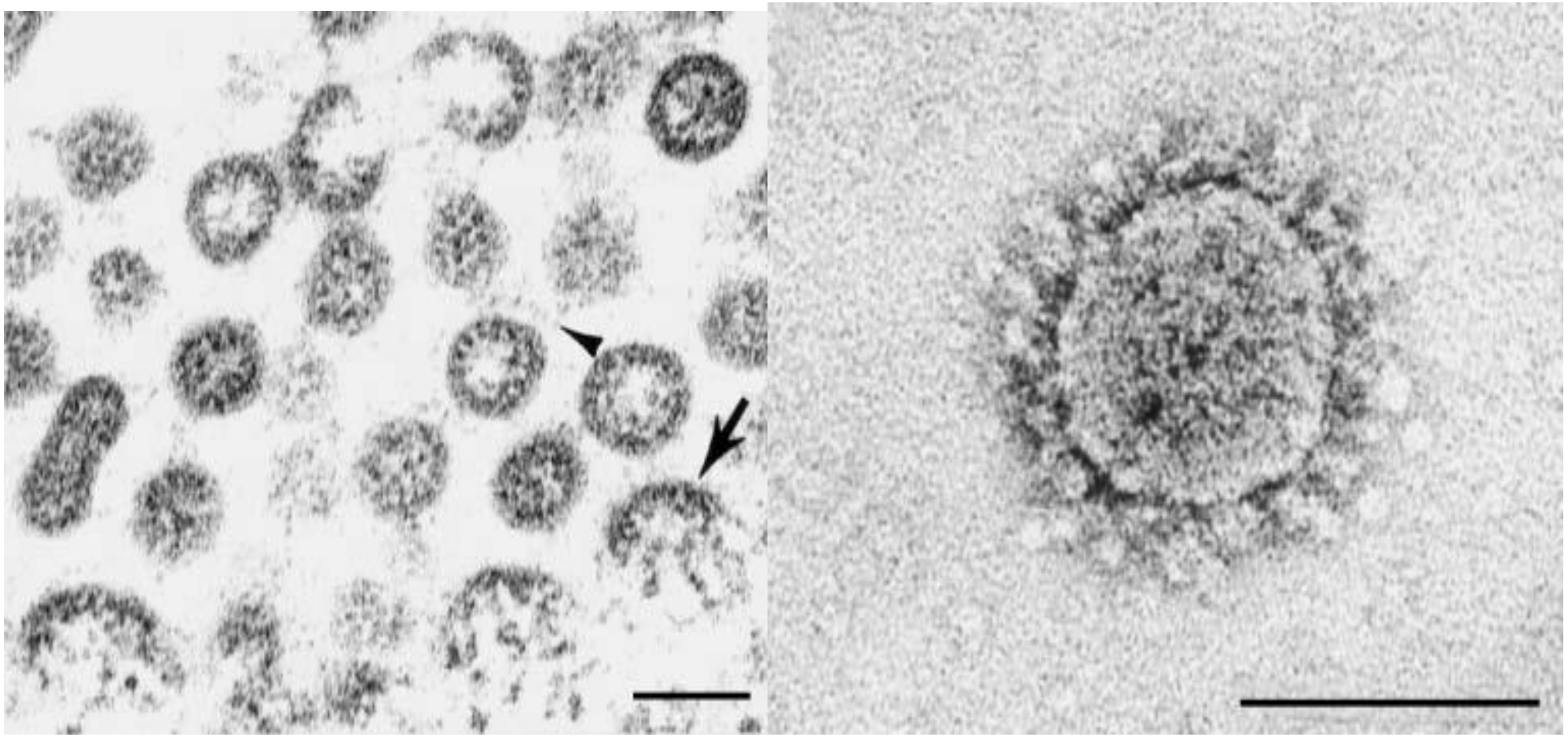
- In late 2002, several hundred of cases of a severe atypical pneumonia were reported in Guangdong Province in the People's Republic of China.
- By March 2003, outbreaks of a similar disease were reported in Hong Kong, Vietnam and Canada.
- In March 2003, the WHO issued a global alert for the illness, called "severe acute respiratory syndrome (SARS).
- By April 2003, over 4300 cases were reported with 250 deaths in over 25 countries of the world.

History continued.

- By March 2003, laboratories in the U.S., Canada, Germany, and Hong Kong isolated a coronavirus from the respiratory secretions of affected patients, designated SARS-CoV in Vero cells.

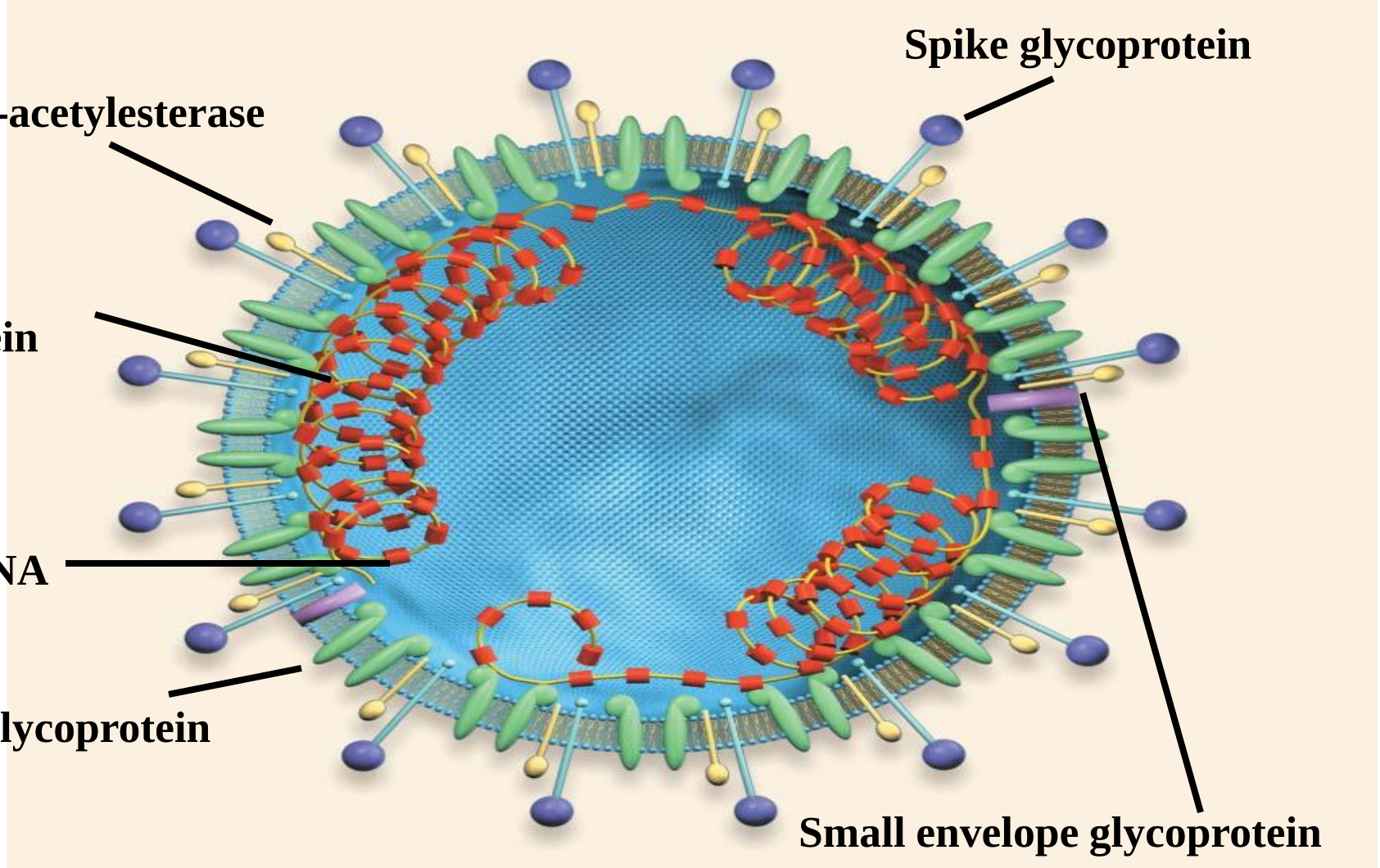
Unique Features of the Outbreak

- First reported outbreak of a human coronavirus producing a pneumonia with a high morbidity and mortality.
- Rapid spread of the virus in the human population.
- Large secondary attack rate in health care providers.



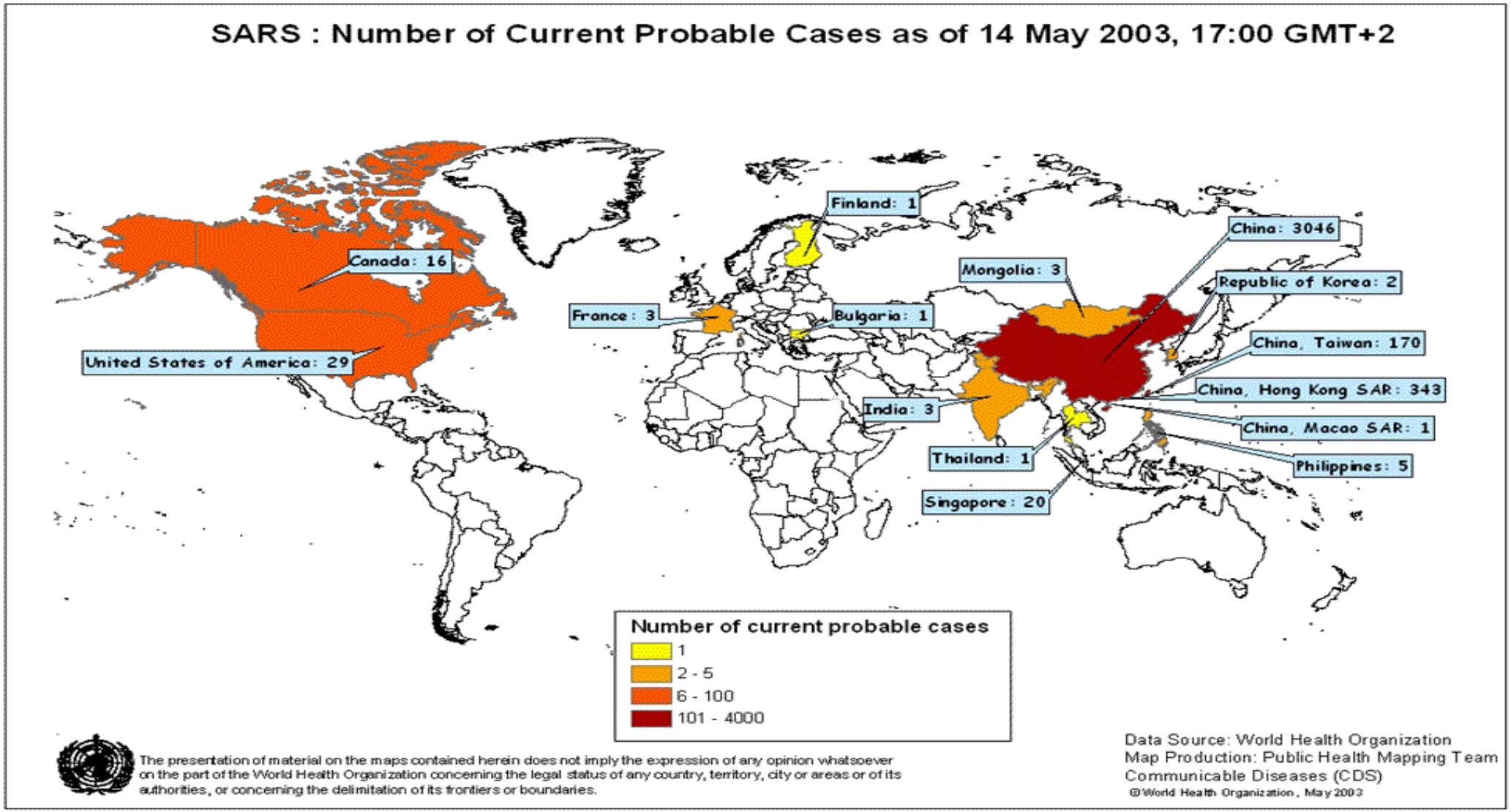
Ksiazek T.G., Erdman D., Goldsmith C.S et al, A novel coronavirus associated with severe acute respiratory syndrome, NEJM, 2003; 348:1953-1966.

Structure of Coronavirus Virion

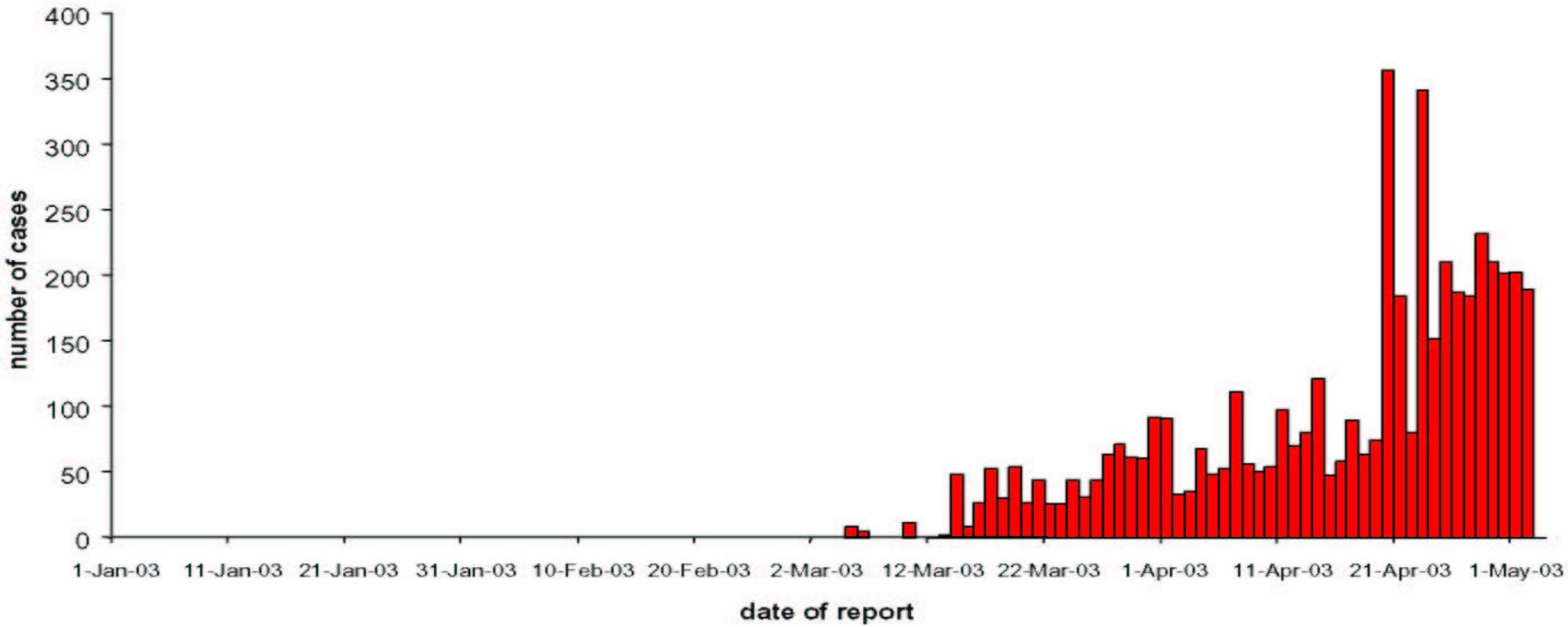


Holmes, K.V. SARS-Associated Coronavirus. NEJM 2003;

Epidemiology of Epidemic



Probable cases of SARS by date of report
Worldwide* (n=4,864)
1 January - 2 May 2003



* Includes all cases from Hong Kong SAR and Taiwan, China, but only those cases elsewhere in China reported after 3 April 2003 (1,190 cases between 16 November 2002 and 3 April 2003 not shown).
The United States of America began reporting probable cases of SARS to WHO on 20 April 2003.

Course of Disease in One Patient

Poutanen SM, Low DE, Henry B et al. Identification of severe acute respiratory syndrome in Canada. NEJM 2003; 348: 1995-2005.

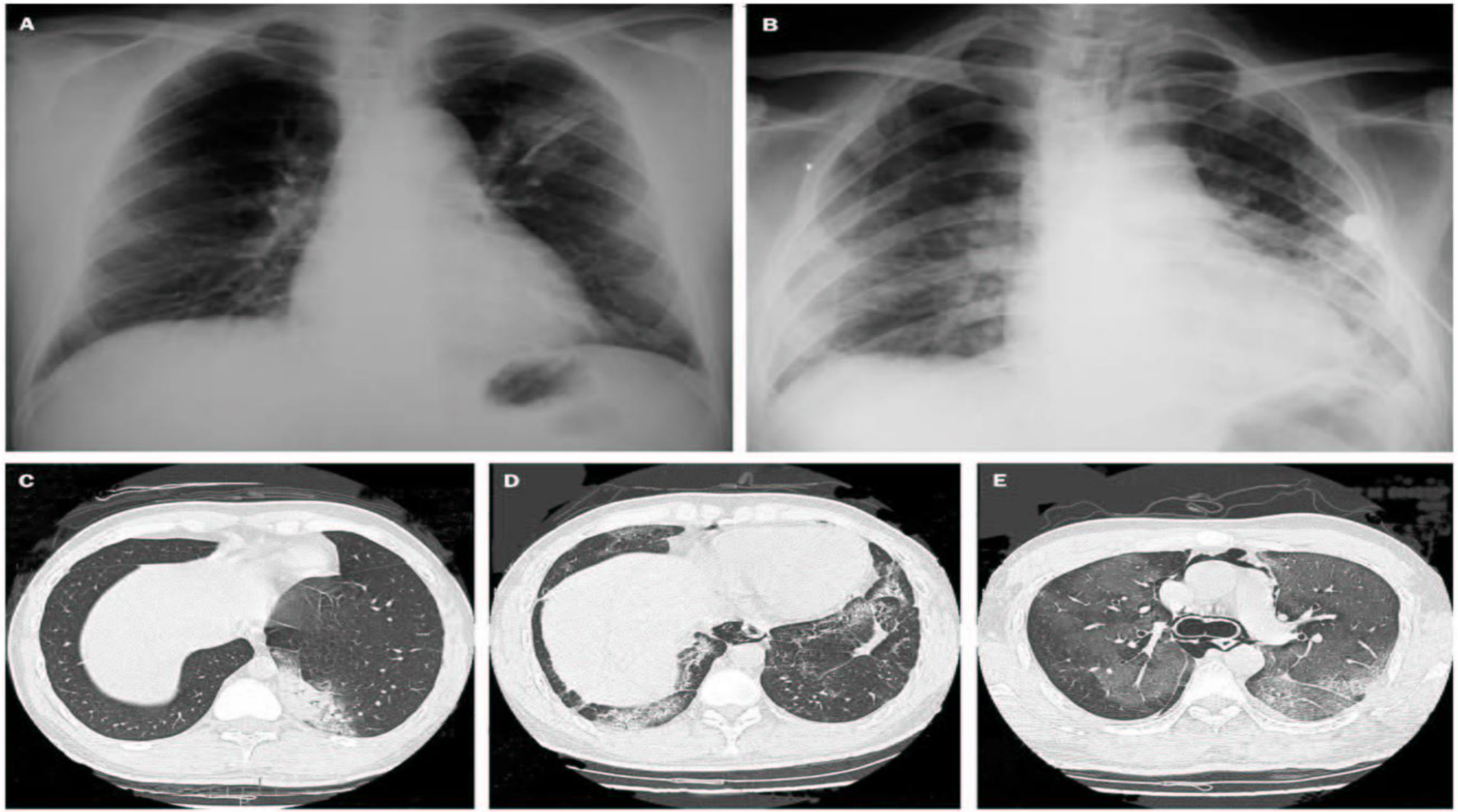


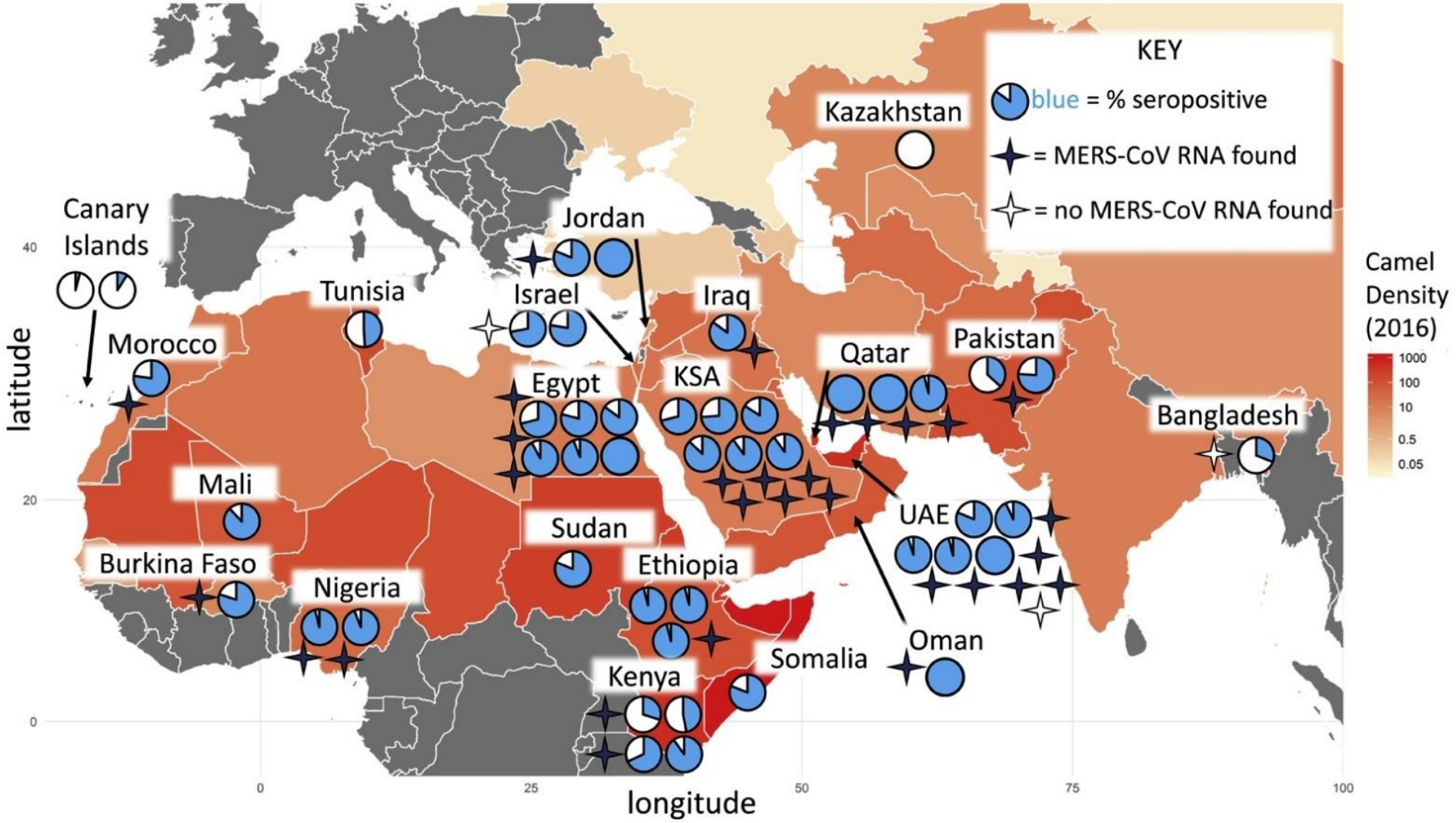
Figure 2: **Chest radiographs and high-resolution CT scans from two SARS patients**

A Man aged 34 years admitted for high fever and cough. A: Consolidation seen in left upper and middle zones, which progressed maximally at day 7. B: At day 20, resolution of consolidation in the left upper and middle zones but new widespread air-space opacities noted; those in left lung base were confluent. Man aged 32 years, presented with fever, chills, rigors and myalgia, with clear chest radiograph at admission. C: High-resolution CT of thorax shows peripheral subpleural consolidation in medial basal segment of left lower lobe. D: Resolution of original left lower-lobe consolidation at day 18. E: Disease complicated by spontaneous pneumomediastinum.

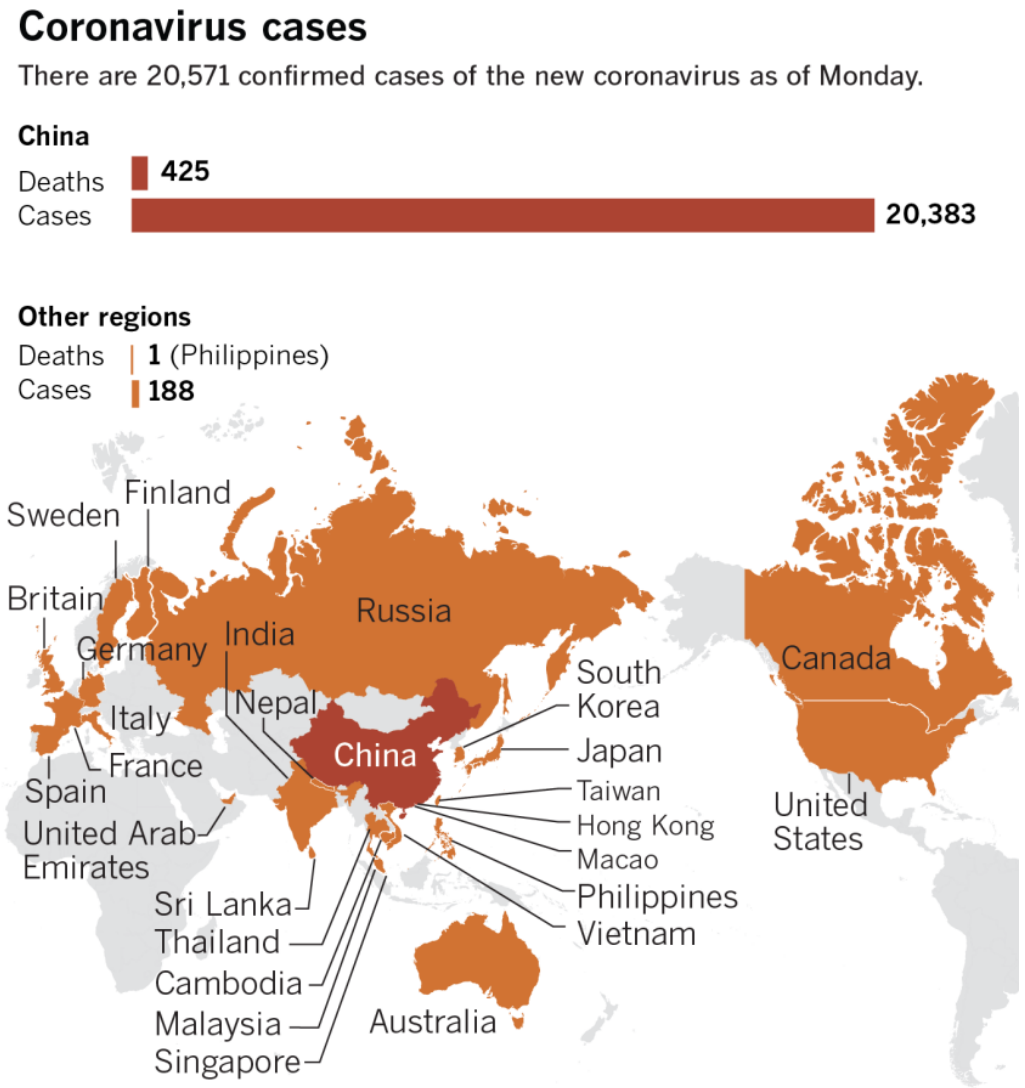
SARS Conclusion

- SARS is an example of a disease that is emerging.
- A unique virus that jumped from animal to man.
- A clinical picture that was consistent with other known viruses such as influenza.
- Rapid spread due to current mobile global society with air transportation.
- Produced tremendous economic loss and social disruption.

Middle Eastern Respiratory Syndrome (MERS Cov)



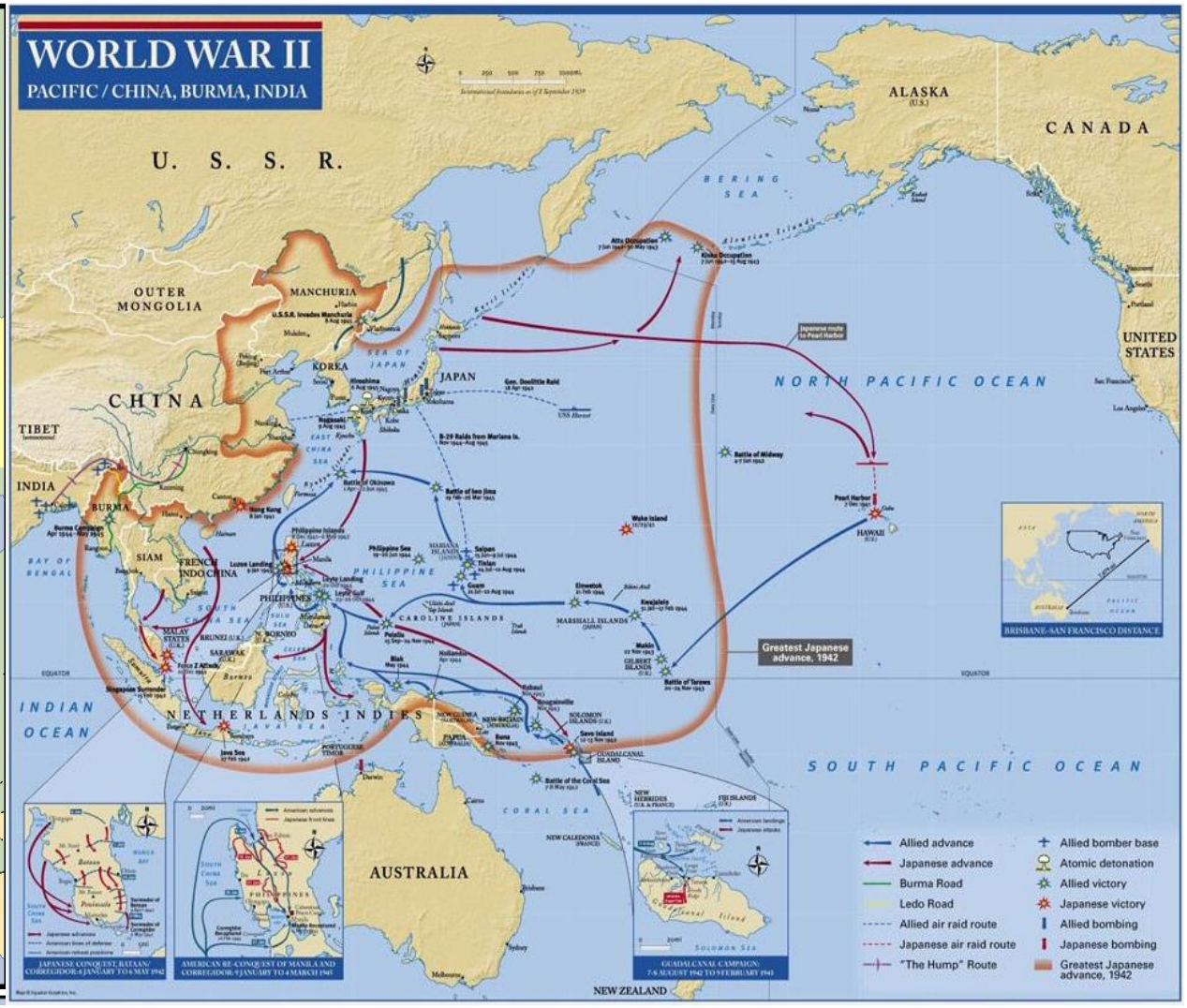
Wuhan CoV (As of 2/4/2020)



World War II

World War II


THE SECOND WORLD WAR
THE EUROPEAN THEATER
1942 - 1945
NORWAY
SWEDEN
FINLAND
IRELAND
DENMARK
GREAT BRITAIN
GERMANY
POLAND
SOVIET UNION
RUSSIA
FRANCE
CZECH Pr.
SLOVAKIA
HUNGARY
ROMANIA
CROATIA
SERBIA
BULGARIA
ITALY
SWITZERLAND
ANDORRA
PORTUGAL
SPAIN
GREECE
TURKEY
ALBANIA
MOROCCO (FRANCE)
ALGERIA (FRANCE)
TUNISIA (FRANCE)
LIBYA (ITALY)
EGYPT
Atlantic Ocean
Mediterranean Sea
Black Sea
Baltic Sea
Adriatic Sea
Aegean Sea
Red Sea
Sahara Desert
English Channel
Invasion of Normandy (D-Day, 6 June 1944)
Battle of the Bulge (D-Day, 6 June 1944)
Kursk, 1943
Anzio, 1944
Salerno, 1943
Invasion of Sicily, 1943
Kasserine Pass, 1943
Tunis, 1943
Mareth, 1943
Tobruk, 1942
From Great Britain
From U.S.
Patton (Nov. 1942)
Ryder (Nov. 1942)
Alexander (Nov. 1942-May 1943)
Fredendall (Nov. 1942)
City or Town
National Capital
National Boundaries
Battle Site
Axis Advance
Allied Advance
Neutral Countries
Axis Controlled (Max. Extent)
Axis
Allies


WORLD WAR II
PACIFIC / CHINA, BURMA, INDIA
U. S. S. R.
ALASKA
CANADA
UNITED STATES
OUTER MONGOLIA
MANCHURIA
CHINA
KOREA
JAPAN
TIBET
INDIA
BURMA
SIAM
FRENCH INDO-CHINA
PHILIPPINES
NETHERLANDS INDIES
AUSTRALIA
NEW ZEALAND
HAWAII
NORTH PACIFIC OCEAN
SOUTH PACIFIC OCEAN
INDIAN OCEAN
BERING SEA
CORAL SEA
Greatest Japanese advance, 1942
BRISBANE–SAN FRANCISCO DISTANCE
Allied advance
Japanese advance
Burma Road
Ledo Road
Allied air raid route
Japanese air raid route
"The Hump" Route
Allied bomber base
Atomic detonation
Allied victory
Japanese victory
Allied bombing
Japanese bombing
Greatest Japanese advance, 1942

Dengue Key Facts

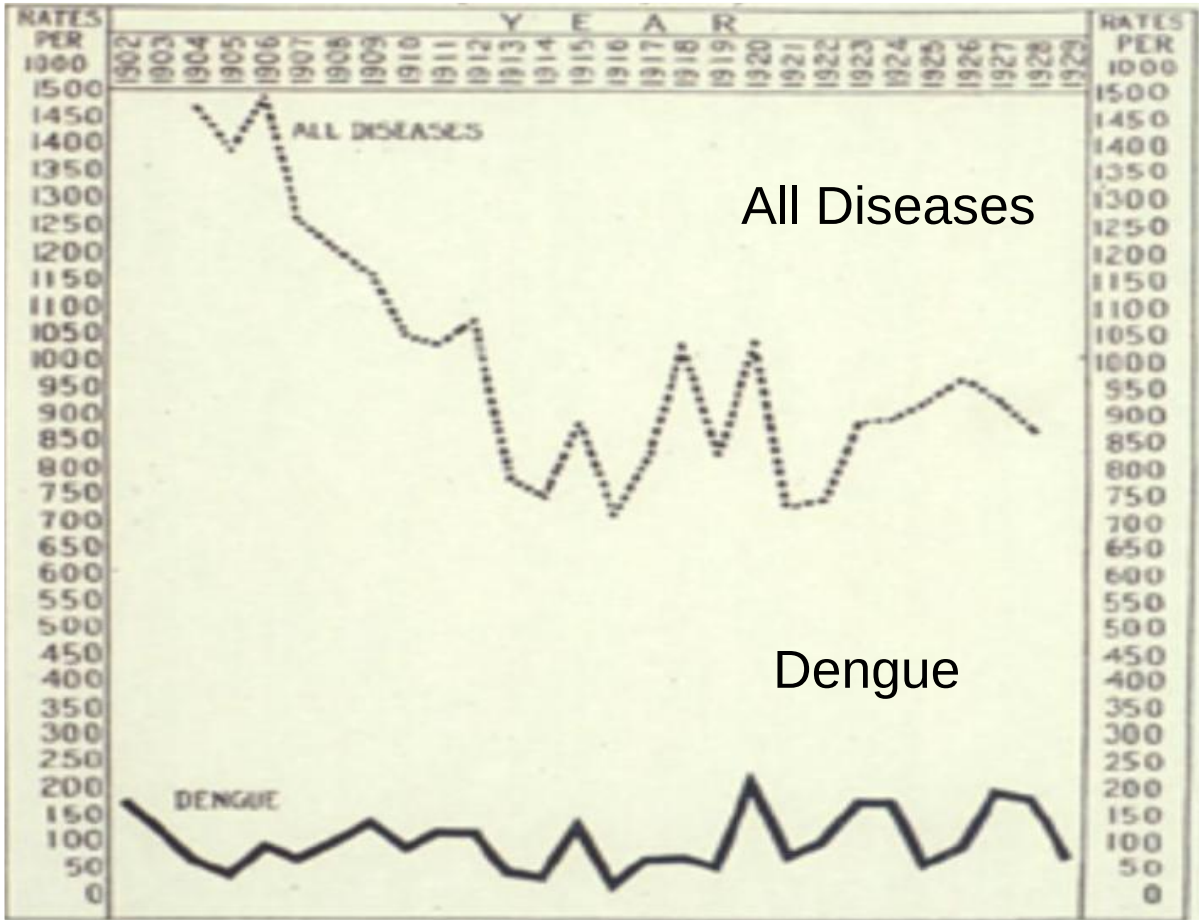
- Mosquito-borne viral infection (*Aedes aegypti*), tropical and sub-tropical regions, urban areas at high risk.
- Global health problem half of the world's population is now at risk-390 million dengue infections per year, 96 million symptomatic.
- Dengue fever is a flu-like illness on 2nd infection can lead to severe dengue.
- There is no specific treatment for dengue/ severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%.
- Vaccines are in clinical trials.

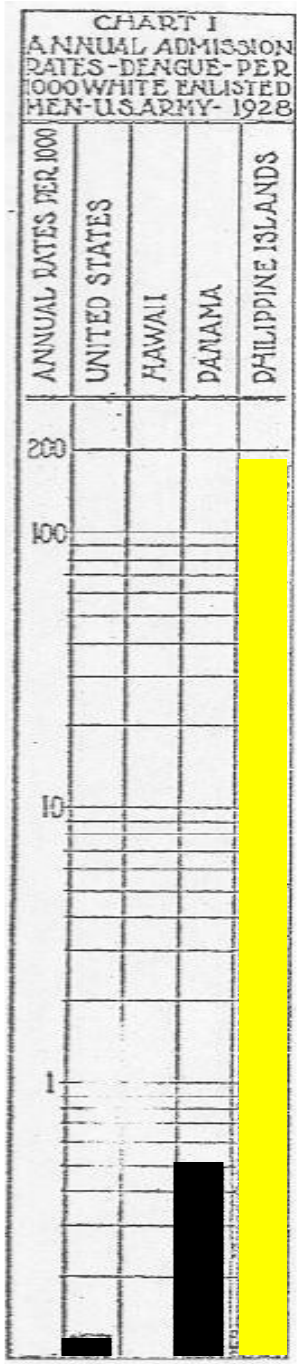
US Dengue Epidemics

- 1780 –
  - Epidemic in Philadelphia described by Dr. B. Rush
  - August-September febrile exanthem
  - Confined to persons residing along the Delaware River
  - The term “Break Bone Fever” becomes popular
- 1800’s –
  - Numerous US Coastal cities suffer epidemics
- 1995 -
  - Texas has 29 cases, 7 locally acquired
- 2001 –
  - Hawaiian Islands report 119 cases of DF
- Majority of cases are imported or in returning travelers

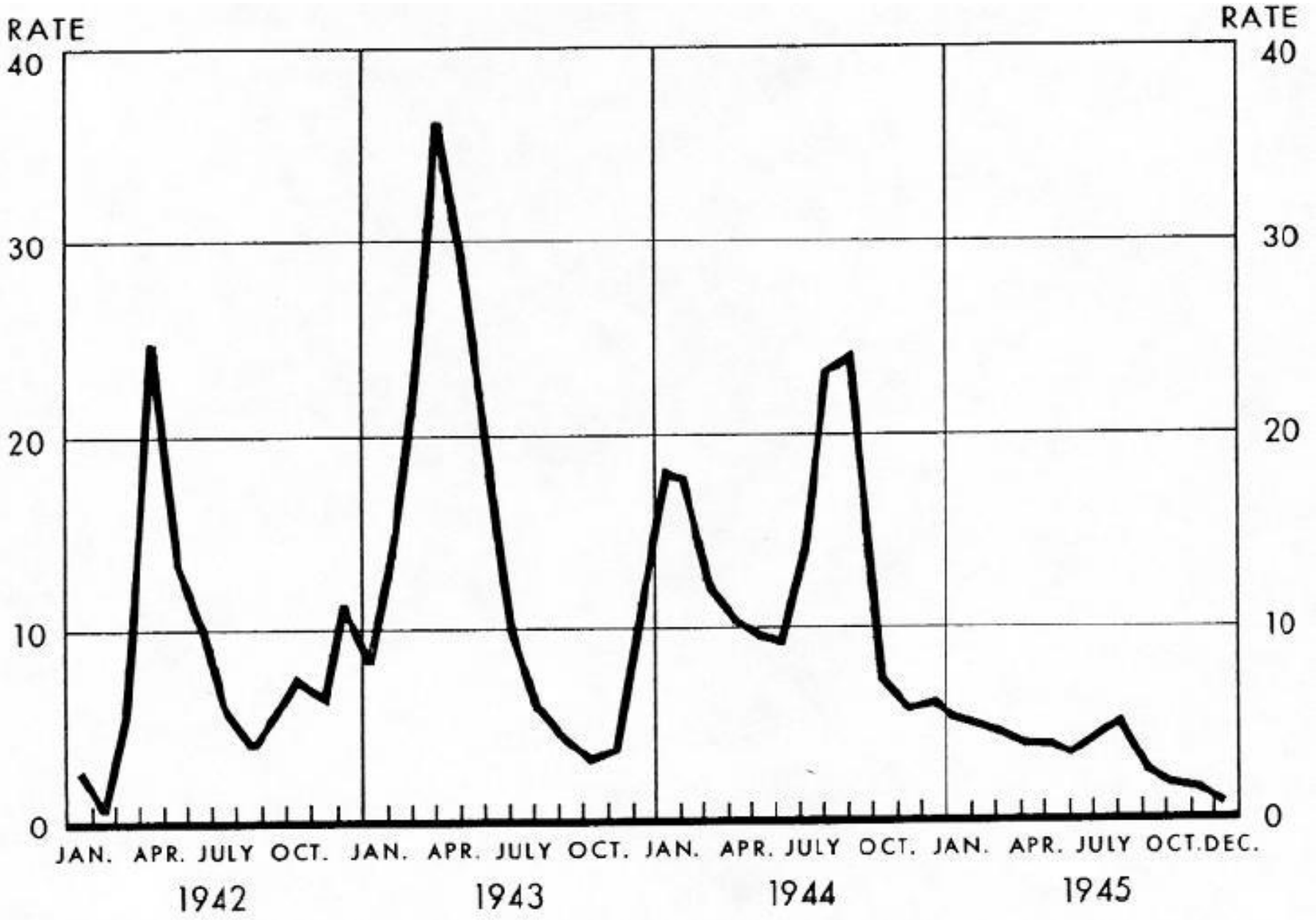
American Soldiers- Philippine Islands, 1902-1928

- Average loss to the Army of 7,715 days per year





Theater or area	1942–45		1942		1943		1944		1945	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Continental United States	75	0.01	6	0.00	25	0.00	19	0.00	25	0.01
Overseas:										
Europe	91	0.02	1	0.01	----------	0	35	0.02	55	0.03
Mediterranean [1]	358	.23	1	.04	84	.18	213	.33	60	.15
Middle East	35	.26	1	.17	24	.45	16	.22	----------	0.00
China-Burma-India	8,217	18.37	73	8.35	999	25.22	5,240	31.06	1,905	8.27
Southwest Pacific	50,903	32.10	4,225	59.32	6,436	33.89	28,292	52.47	11,950	15.21
Central and South Pacific	29,941	20.79	19	.13	11,650	39.96	16,442	37.48	1,830	3.27
North America [2]	3	.01	----------	0	3	.02	----------	0	----------	0
Latin America	245	.64	120	1.18	49	.41	46	.54	30	.42
Transports	993	------	2	------	60	------	826	------	105	------
Total overseas [3]	90,786	8.61	4,442	7.58	19,305	11.44	51,104	13.38	15,935	3.58
Total Army	90,861	3.59	4,448	1.37	19,330	2.81	51,123	6.56	15,960	2.15


RATE
40
30
20
10
0
RATE
40
30
20
10
0
JAN. APR. JULY OCT. JAN. APR. JULY OCT. JAN. APR. JULY OCT. JAN. APR. JULY OCT. DEC.
1942
1943
1944
1945

Daily Reported Cases During the Saipan Dengue Epidemic September – October, 1944

- Dengue appears after 15 June island assault
- By 11 August *Aedes* species are numerous (rainy season)
- Combat operations created numerous breeding habitats

Date	Number	Date	Number
1944		*1944*—Continued	
September 14	393	September 26	62
15	426	27	87
16	294	28	79
17	306	29	71
18	289	30	44
19	275	October 1	36
20	230	2	33
21	137	3	27
22	137	4	28
23	112	5	32
24	93	6	23
25	81		

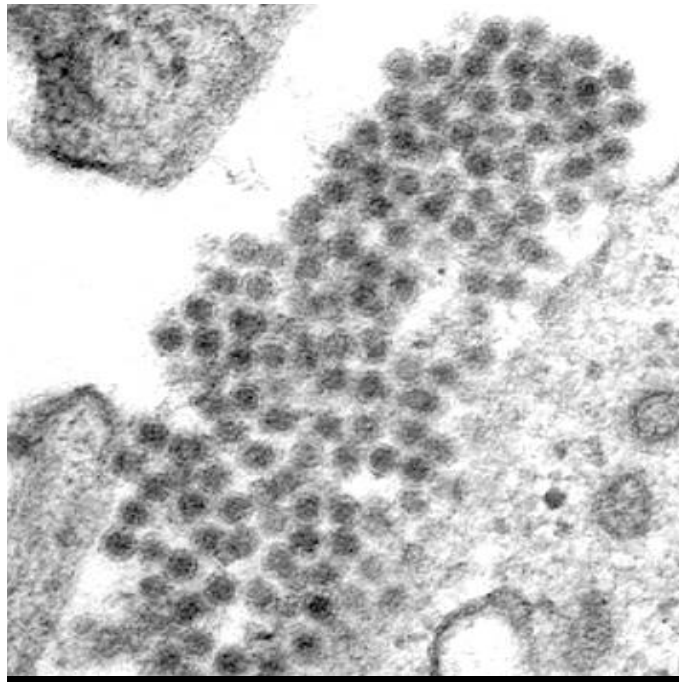
[1] Cases include Army, Navy, and Marine Corps personnel.

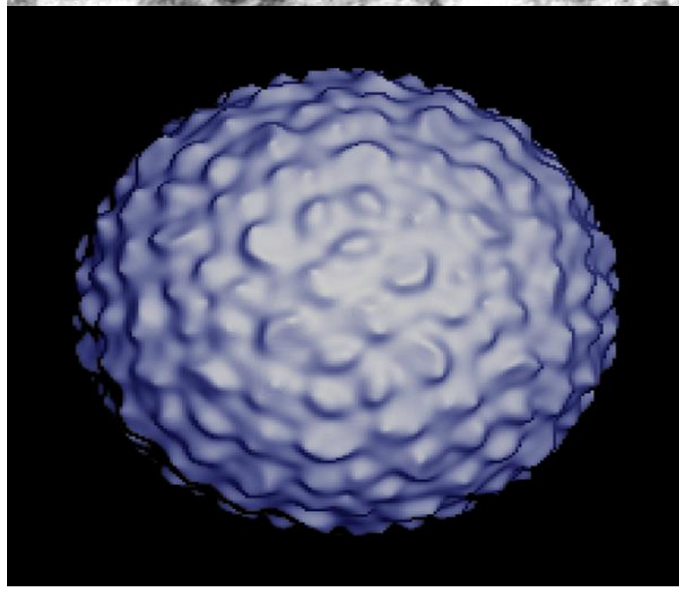
Recent US Military Experience with Dengue

- 1966 - Long Binh, Viet Nam (*Annals* 1967; 66 (6): 1129-1143)
  - 110 Cases of FUO at 93rd Evacuation Hospital
  - Dengue responsible for 31 (28%)
- 1992 - Somalia (*AJTMH* 1995; 53(1):89-94)
  - 289 febrile troops hospitalized
  - 129 (45%) without an identified cause
  - Dengue virus was recovered from 41 (43%) of 96
  - 18 (49%) of 37 culture-negative cases, + IgM ab
- 1997 - Haiti (*JAMA* 1997; 277(19))
  - Febrile illnesses in 103 (25%) of 406 hospital admissions
  - 30 patients demonstrated to have DF

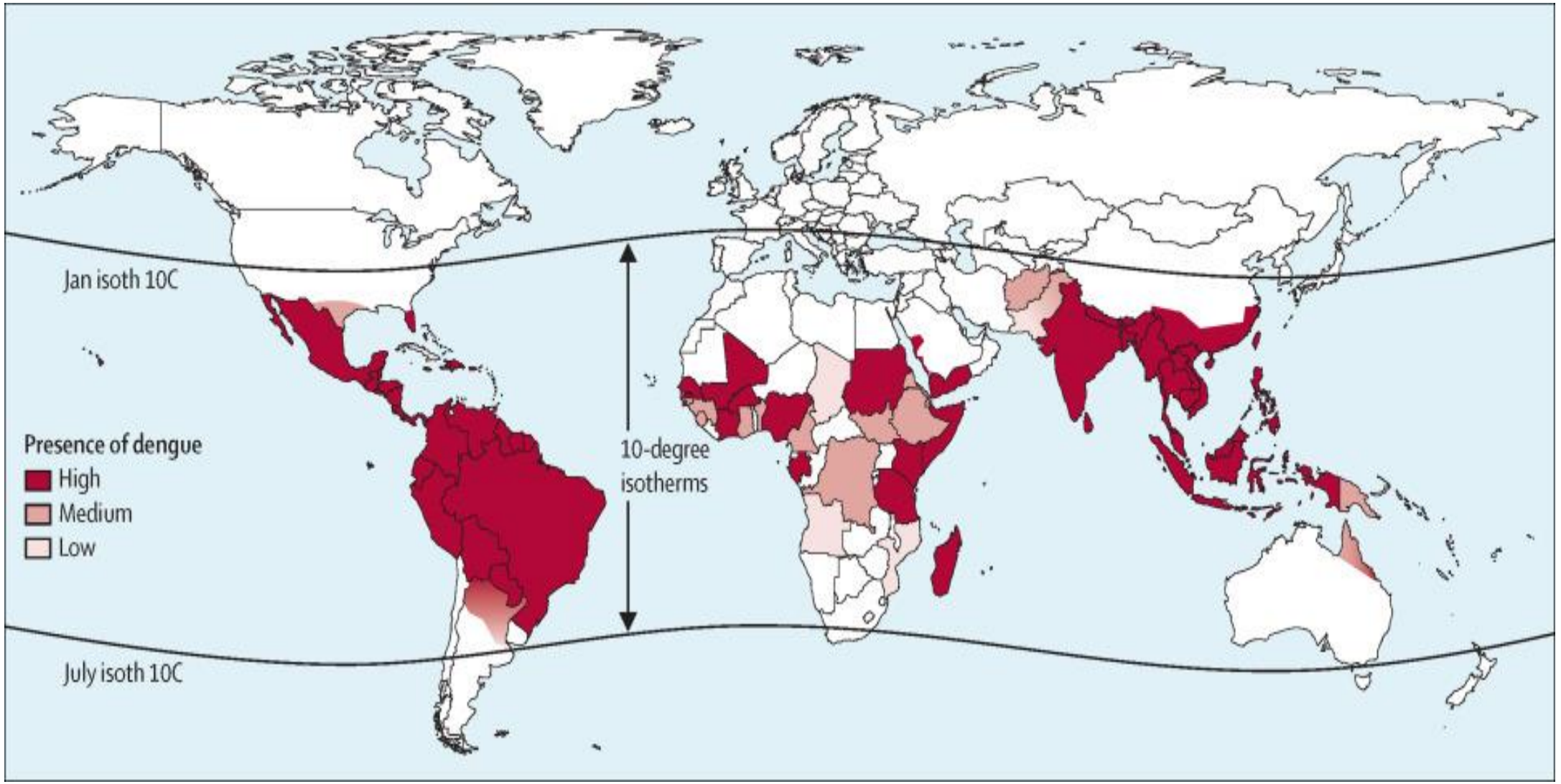
Dengue Viruses

- Genus *Flavivirus* & Family *Flaviviridae*
- Four serotypes
  - DEN-1, -2, -3, and -4
  - Antigenically distinct
- Genetic diversity and phylogenetics
  - 3-5 DEN-1 genotypes
  - 5-6 DEN-2 genotypes
  - 4 DEN-3 genotypes
  - 2 DEN-4 genotypes
- Variations in virus virulence
  - RNA virus mutations
  - Recombination events





Global Distribution of Dengue



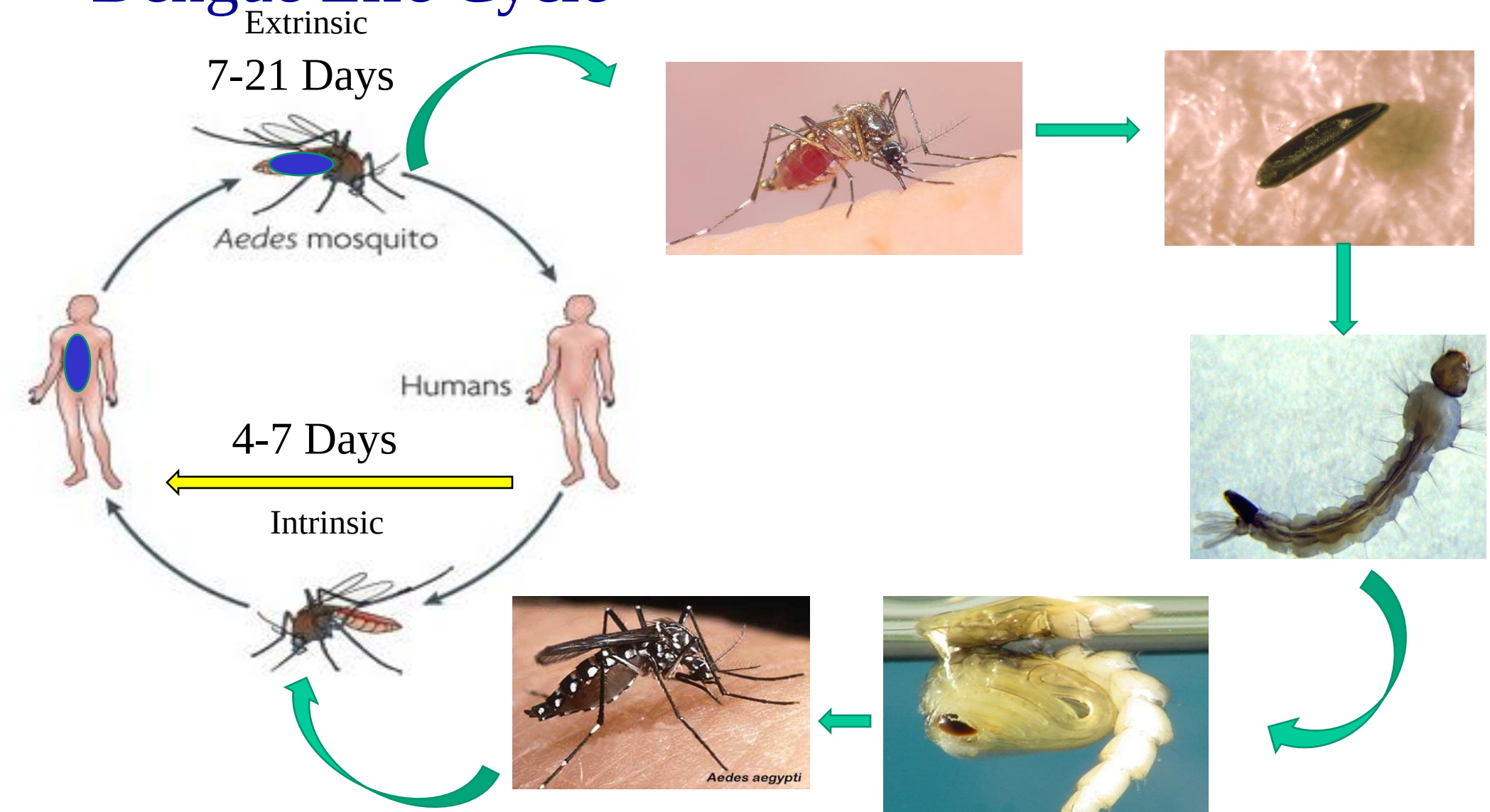
Guzman and Harris Lancet, Vol 385 January 31, 2015

Mosquito-borne Virus (Arbovirus)

Aedes aegypti

Aedes albopictus

Dengue Life Cycle



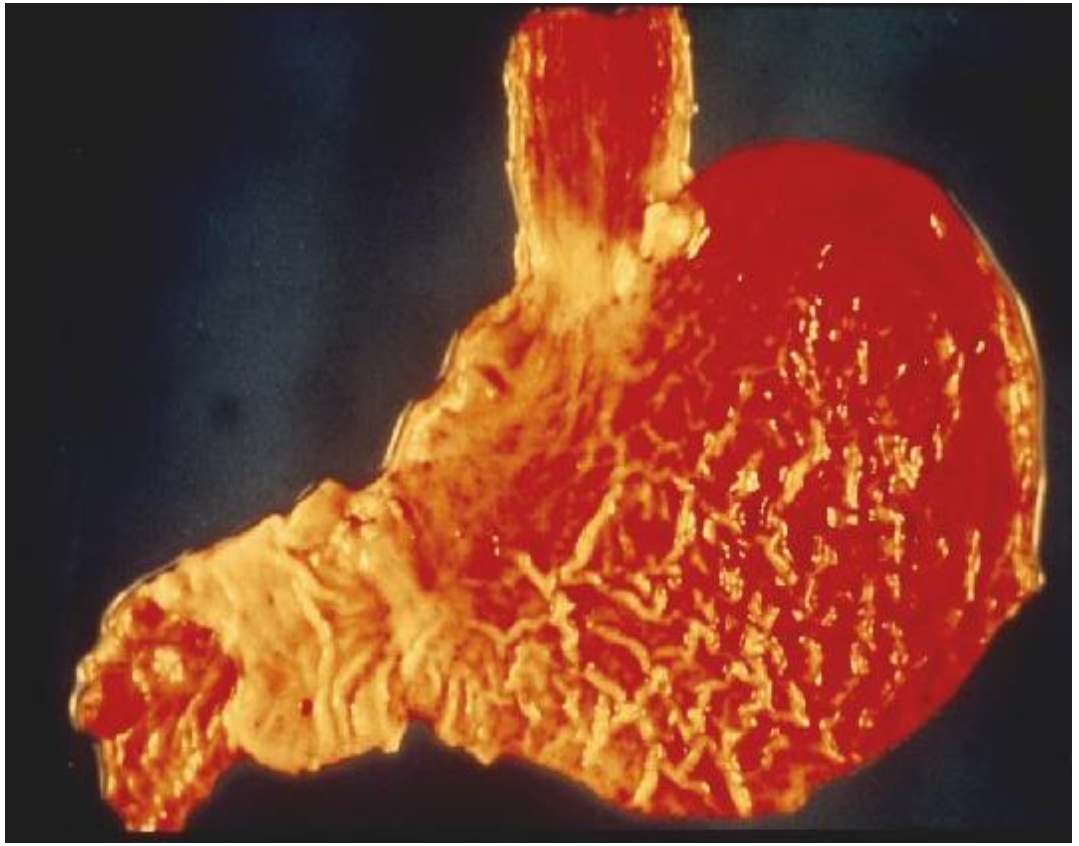
Petechiae on chest wall in child with DHF.

Subcutaneous hemorrhage in child with DHF.

Petechiae on soles of feet in child with DHF.

Showering of petechiae following blood pressure cuff inflation in child with DHF.

Melena



Gastric Bleeding

Shock Syndrome

- Shock syndrome is the severe form of viral hemorrhagic fever and results from:
  - intravascular volume depletion from plasma leakage into the third space and/or blood loss.
  - cardiovascular collapse.

Protecting Your Soldiers From Dengue

- There is no vaccine or therapeutic.
- Personal Protective Measures:
  - Insect repellent (DEET, Picaridin
  - Long sleeves and pants.
  - Screens on windows.
  - Eliminating water sources in and around home ie flower pots, beer bottles, used tires.
  - Eliminate mosquitoes in the home using insecticide.
  - Maximize protection during daytime (feeding time for *Aedes aegypti*).

Korean War

Military Significance

During the Korean War in 1951, military physicians observed the occurrence of a hemorrhagic fever in United Nations forces.

- United Nations forces were under extreme stress from intense combat, combat injuries and environmental conditions. Non-battle injuries included a new type of hemorrhagic fever.

On 22 December 1951, a symposium was held on epidemic hemorrhagic fever in the Far East Command convened by BG William E. Shambora, Chief Surgeon, Far East Command.

COL Joseph H. McNinch, Chief, Preventive Medicine Division, Office of Chief Surgeon, Far East Command, introduced the symposium and writes,

"Today we have before us for discussion a disease entity which has created intense interest among both medical and lay personnel in the Far East Command. During the month of June 1951 there were admitted to the United States medical installations in Korea several patients with an acute febrile disease presenting a combination of symptoms and signs not previously encountered among United Nations personnel in Korea. The symptoms included malaise, weakness, chills, fever, headache, (especially retrobulbar ache), blurred vision, nausea, and vomiting. These symptoms were associated with manifestations of hemorrhagic diathesis: petechial rash, marked injection of the conjunctiva, hematuria, and hematemesis."

Epidemic Hemorrhagic Fever, United Nations Forces in Korea, 1951-52.

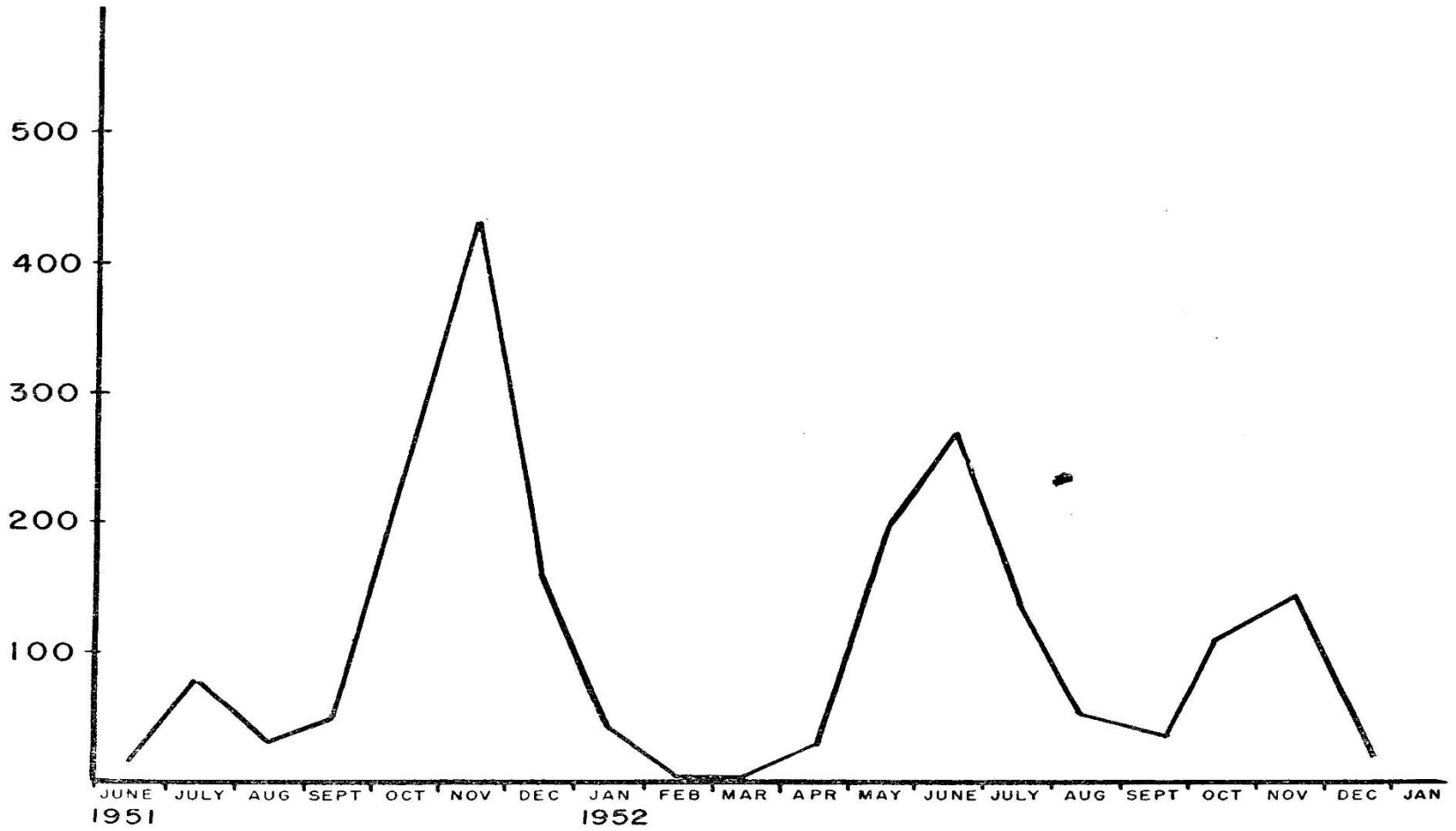


Figure 2. Epidemic hemorrhagic fever, United Nations Forces in Korea, 1951–52, cases admitted to American hospitals.

- The Korean War resulted in over 3,000 United Nation soldiers developing hemorrhagic disease with renal failure, shock and death in 10-15% of cases.
- The etiologic agent of this disease in Korea was isolated in 1967 from the rodent *Apodemus agrarius* and named Hantaan virus after the Hantaan River.

Hemorrhagic Fever with Renal Syndrome (HFRS)

- HFRS is produced by viruses in the family Bunyaviridae, genus *Hantavirus*.
- Specific viruses in the genus *Hantavirus* are Hantaan, Puumala, Seoul, Dobrava Belgrade and Saarema viruses.
- All have a specific geographic location as determined by its rodent host.
- Hantaan virus occurs in Eastern Asia, Puumala virus in Northern and Eastern Europe, Seoul virus in Asia and Dobrava Belgrade and Saarema virus in Central Europe

Clinical Course

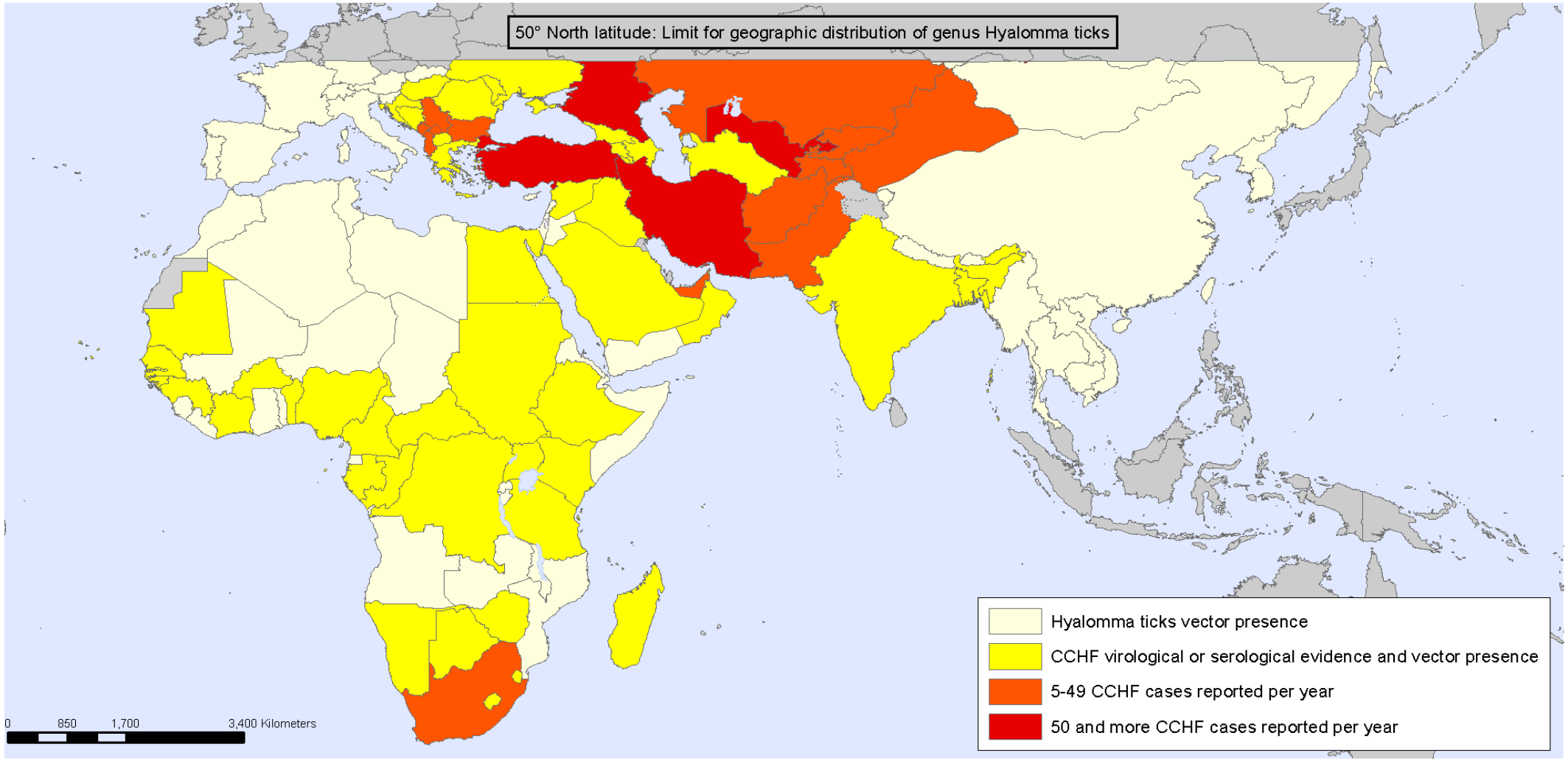
- Characterized by an abrupt onset of fever with severe headache, myalgia and back and abdominal pain.
- Onset of hemorrhage, elevation of liver enzymes and acute renal failure (oliguric followed by a polyuric phase).
- Renal biopsy revealed acute tubular necrosis with interstitial cell infiltration and edema.
- Common cause of death is shock, respiratory failure and pulmonary hemorrhage with a case-fatality between 5%-15%

Summary

- HFRS was a significant military disease during the Korean War.
- Between 5-10 U.S. soldiers in Korea develop HFRS every year.
- Military scientists contributed to the understanding of the epidemiology, risk factors, transmission and pathogenesis of this disease.
- Identified an active antiviral drug and are developing a vaccine against these viruses.

Other Viral Hemorrhagic Fever Viruses

Geographic distribution of Crimean-Congo Haemorrhagic Fever



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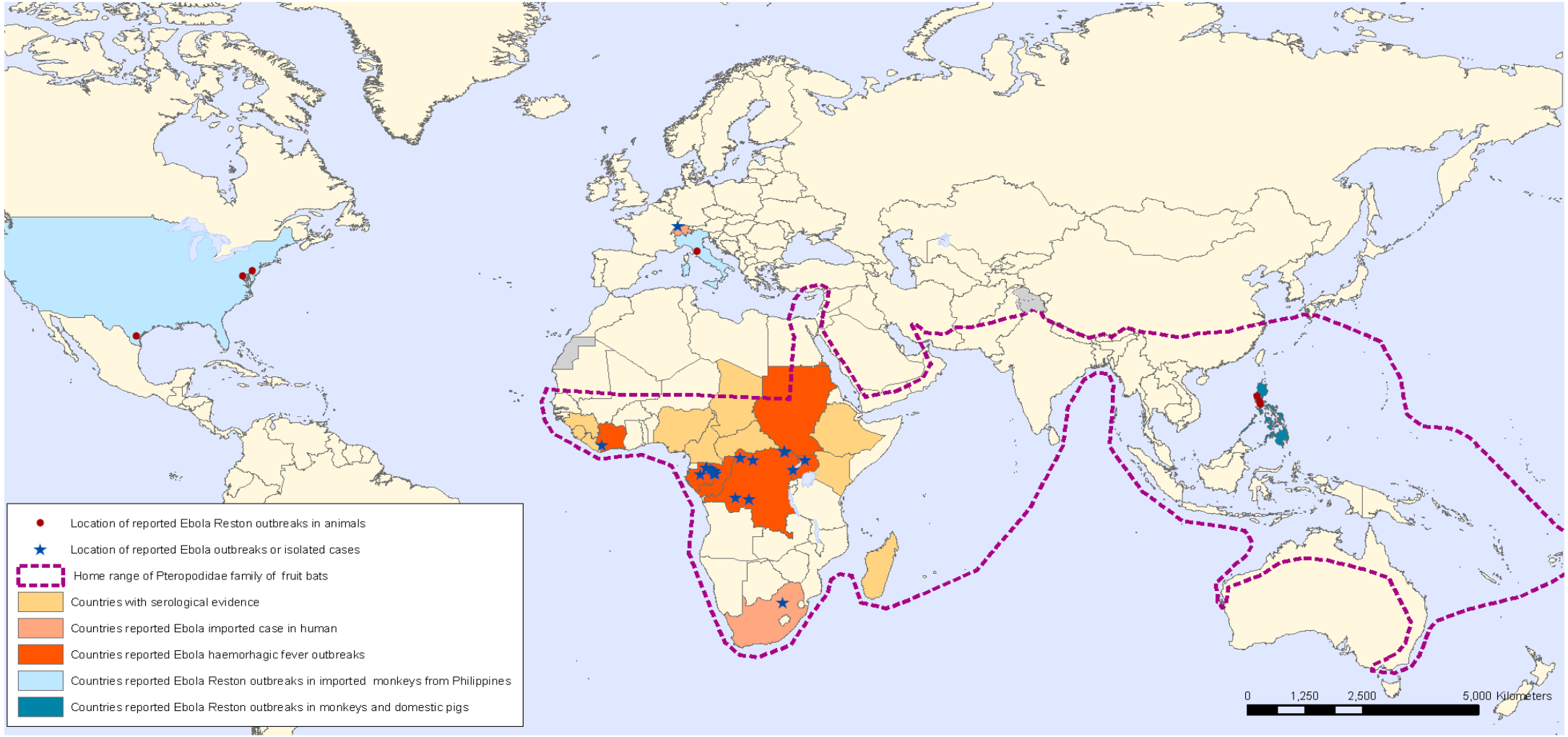
Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Geographic distribution of Ebola haemorrhagic fever outbreaks and fruit bats of Pteropodidae Family



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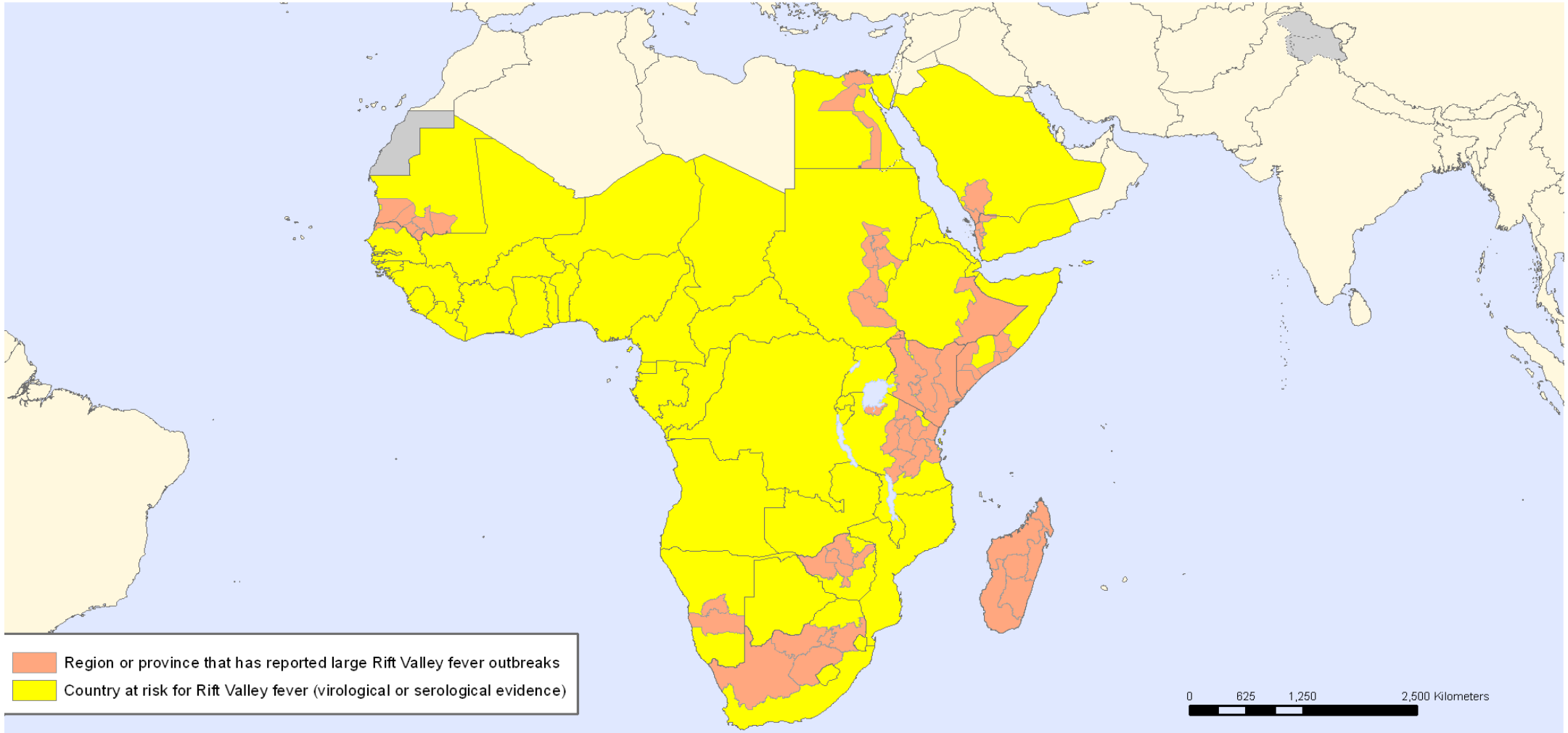
Data Source: Global Alert and Response Department
World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Geographic distribution of Rift Valley fever outbreaks



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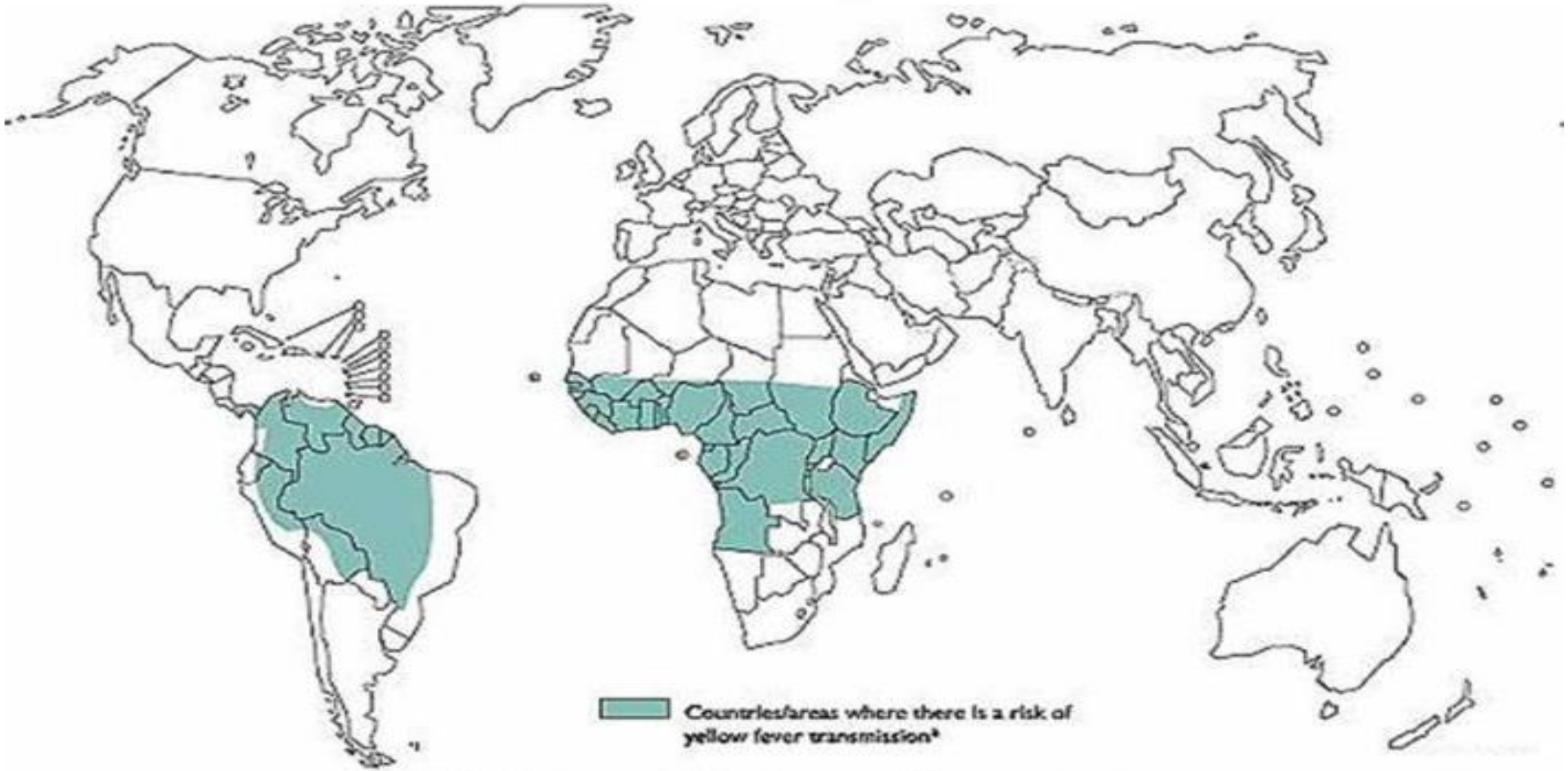
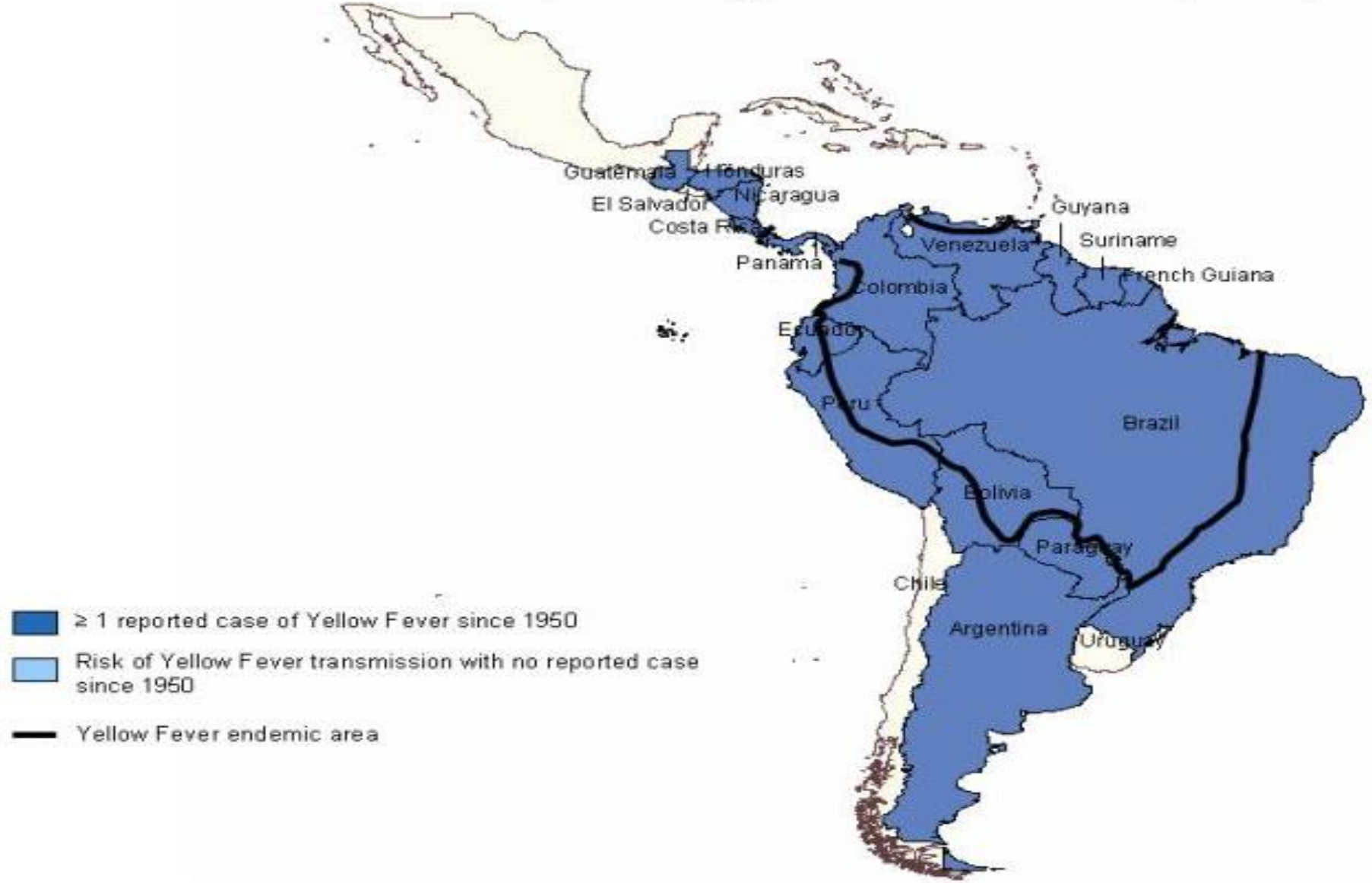
Areas at risk of Yellow Fever transmission

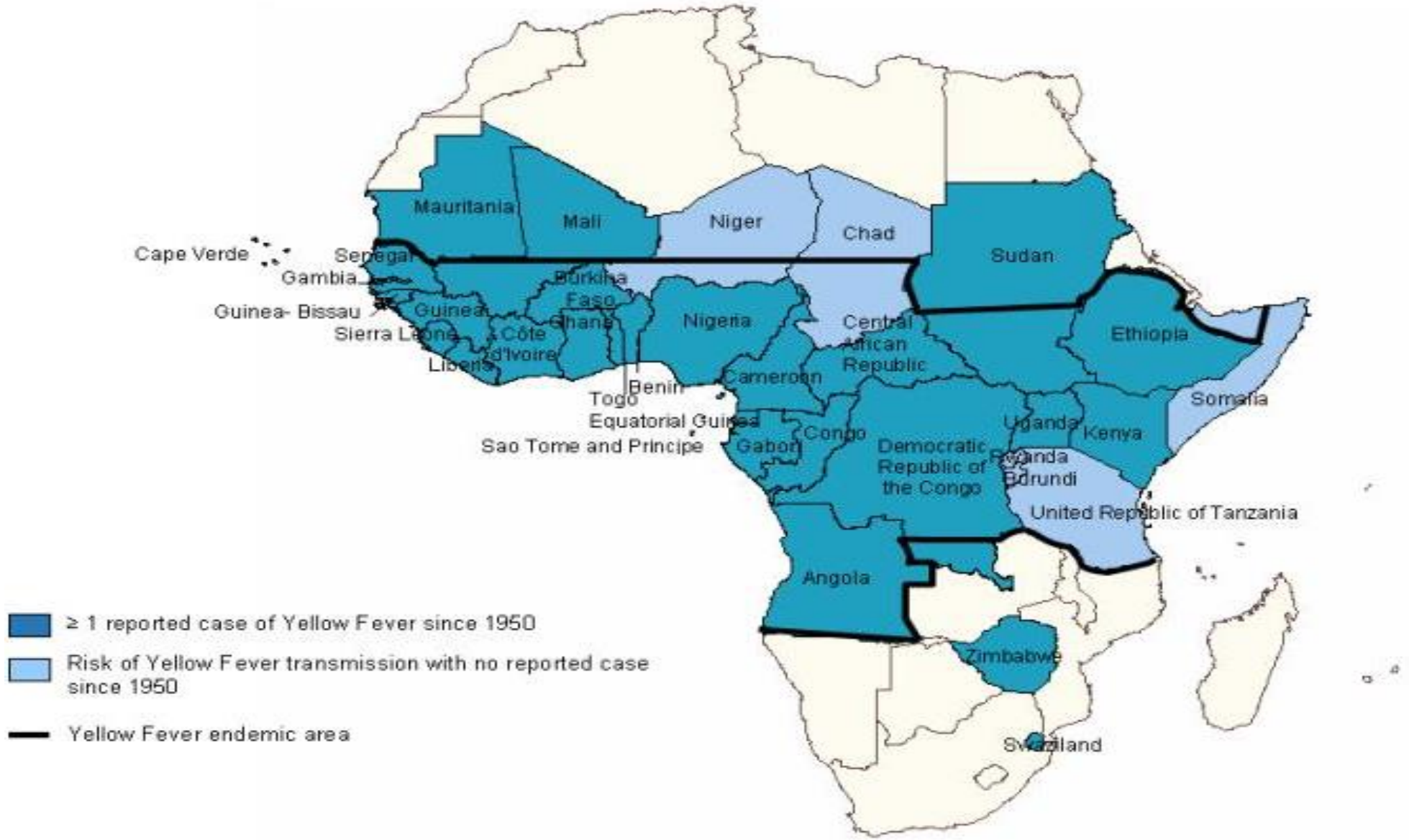


* Either yellow fever has been reported or the presence of vectors and animal reservoirs creates a potential risk of infection (considered to be endemic areas).

Yellow Fever epidemiology in America at country level, 1950- 2004



Yellow Fever epidemiology in Africa at country level, 1950- 2004

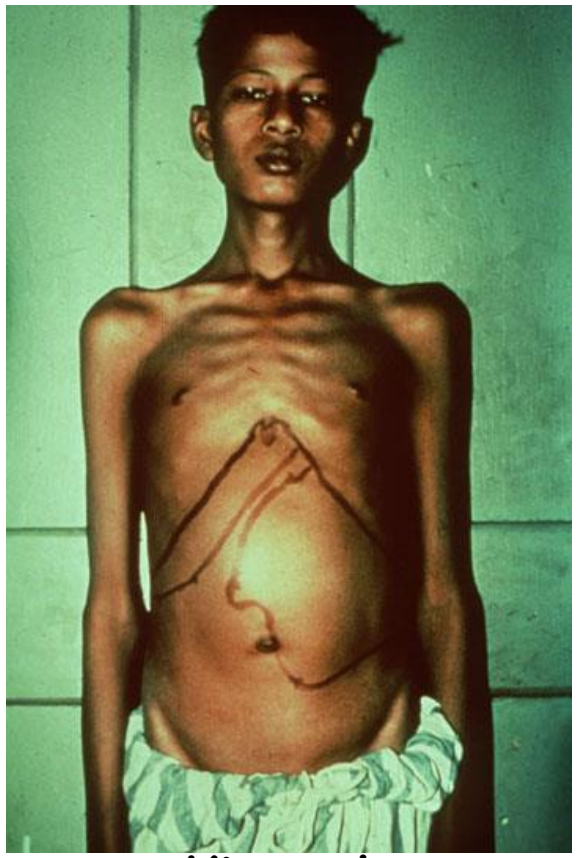


Iraq War

- 22 year old black male SFC, US Army, in otherwise good health, was deployed in Iraq, north of Baghdad for 6 months.
- No acute illness while in Iraq, noted numerous insect bites, was without bednets or DEET for the past 3 months.
- 2 months noted these papules which turned into an ulcer without healing.
- Denies pain, tenderness or fevers associated with the ulcers.

US Army special forces soldier
Presents to ‘TMC” in Bagram, Afghanistan Feb 02
2 week history of expanding ulcer on back of leg

3 Major Clinical Syndromes

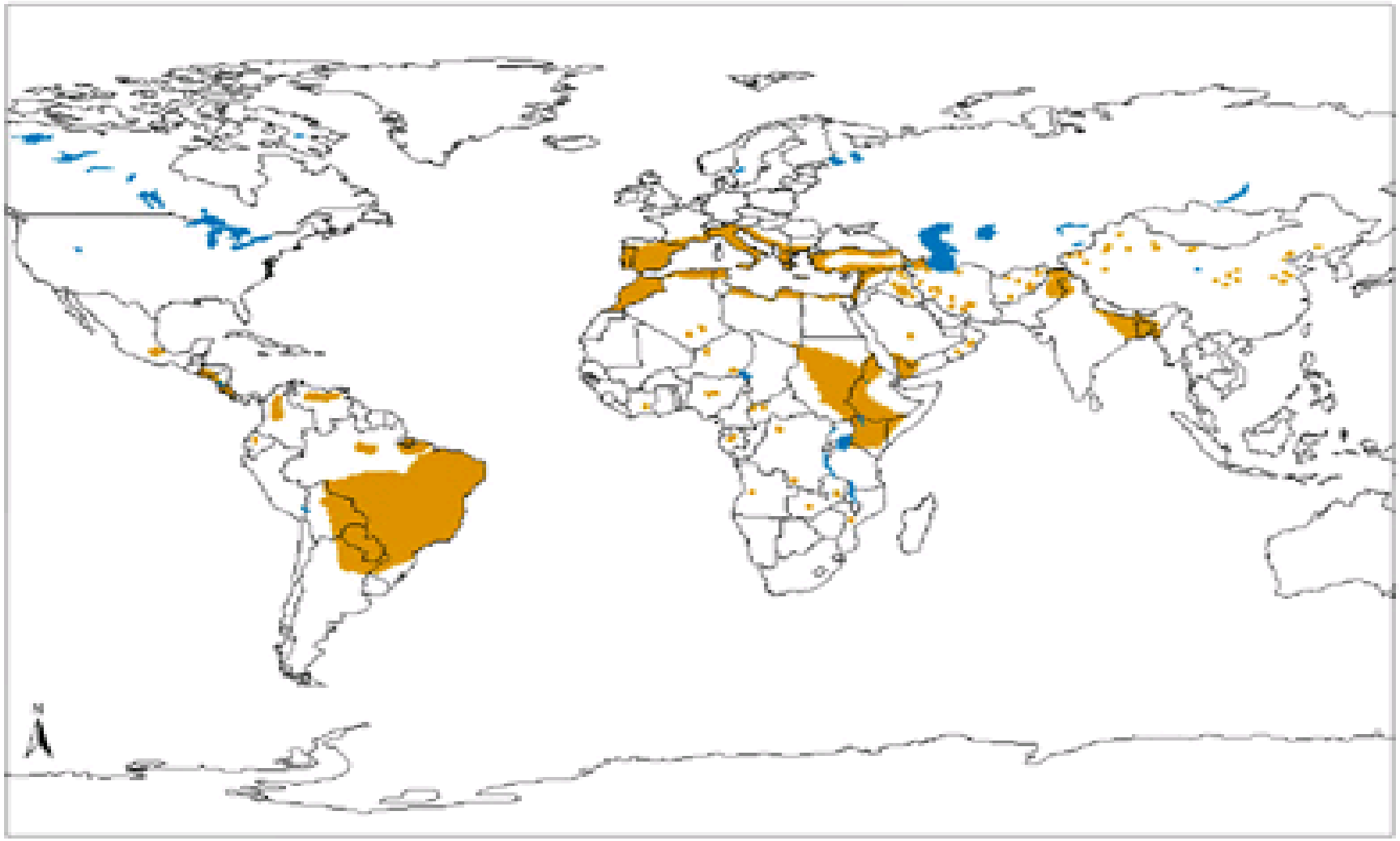


Visceral Leishmaniasis

Cutaneous Leishmaniasis

Mucosal Leishmaniasis

Geographical distribution of visceral leishmaniasis in the Old and New World



Geographical distribution of cutaneous and mucocutaneous leishmaniasis in the New World

http://www.who.int/emc/diseases/leish/leisgeo1.html


1
2
3
4

Leishmaniasis as a Military Threat

- WWII - Karum river valley (Iraq)
  - 630 cases of CL in US forces in 3 months
- 1967 - Israeli Defense Force near Jericho
  - Scores of cases, 50% attack rate
- 1984 - Puerto Rican NG at JOTC, Panama
  - 14 / 64 (22%) cases of CL
- 1986 - 484 cases in Guatemalan Army
  - 1-2% of force, morale problem

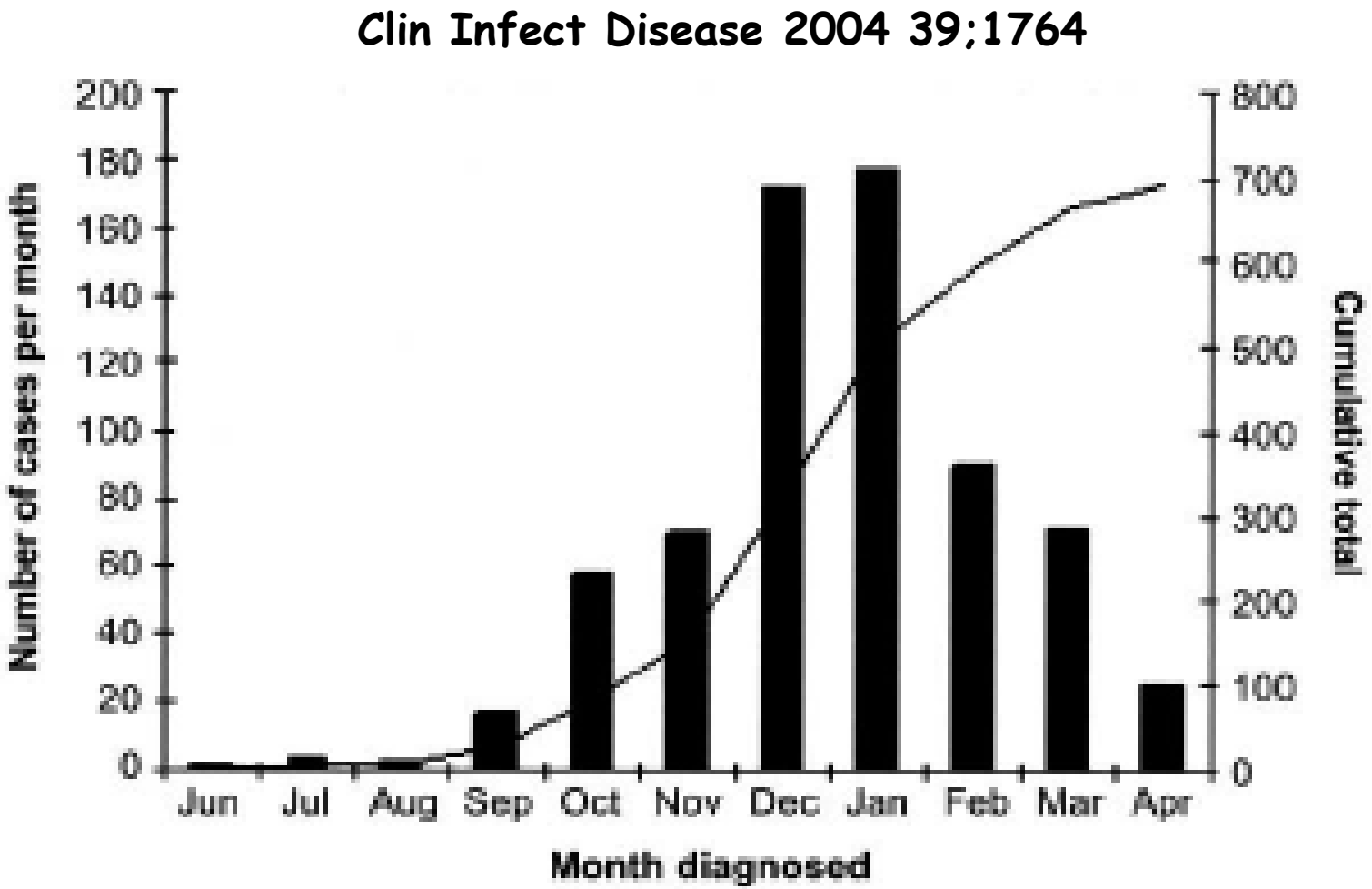
Leishmaniasis as a Military Threat

- 1990 - Multinational force in the Sinai
  - 113 cases of CL per 1,000 peace keepers
- 1990 - Canadian paratroopers in Guyana
  - 17 / 27 (63%) cases of CL in 6 hours!
- 1992 - Colombian Army
  - 3,000 cases of CL reported
- 1992 - Jungle training in French Guiana
  - 6 / 12 (50%) cases of CL in USMC in 2 weeks

Leishmaniasis as a Military Threat

- 1992 - ODS
  - 12 cases of viscerotropic leishmaniasis caused by *L. tropica*
  - 20 cases of CL
- 1980s to present
  - Thousands of cases of CL in Iranian and Iraqi forces during border war
  - Approximately 1,000 cases treated in US Soldiers during the Iraq War.

CL Epidemic Curve from OIF1



Summary of OIF1:Sep 2003 - May 2004

- Cutaneous Disease
  - 1,178 cases confirmed from OIF1
  - Virtually all from Iraq, redominantly *L. major*
  - Estimated 20,000 lost duty days and a cost of >$10 million
- Visceral Disease
  - 4 cases (2 Afghanistan, 2 Iraq)
    - 1 case presented 14 months after leaving Afghanistan
    - 1 Iraq case from the Green Zone

Protecting Soldiers

- Permethrin impregnated bednets and uniforms are of benefit.
- DEET
- Long sleeves and pants tucked into boots.

War in Afghanistan

- 27 y/o white male, US Army soldier on his way back from a forward operating base in Afghanistan.
- On his trip back he developed tingling sensation and pain in his right hand. He presented to the E.R. and diagnosed with a tendonitis and given NSAIDs.
- In the next 48 hours he developed fever, headache and neck stiffness and presented to the E.R. where a clinical diagnosis was made.
- His history is notable for a dog bite he had in his right hand in Afghanistan 7 months ago. There was no documentation that he was given RIG or rabies vaccine and he had no rabies vaccine prior to his deployment.

Course of Illness

HD 1: Admitted with hydrophobia and aerophobia.

HD 2: Bx of nape of neck ag pos for rabies, CSF and saliva PCR positive for rabies virus.

HD 3: Cerebral edema from rabies encephalitis, received EVD and ICP monitor. Started on Milwaukee Protocol.

HD 4: Respiratory failure, ARDS.

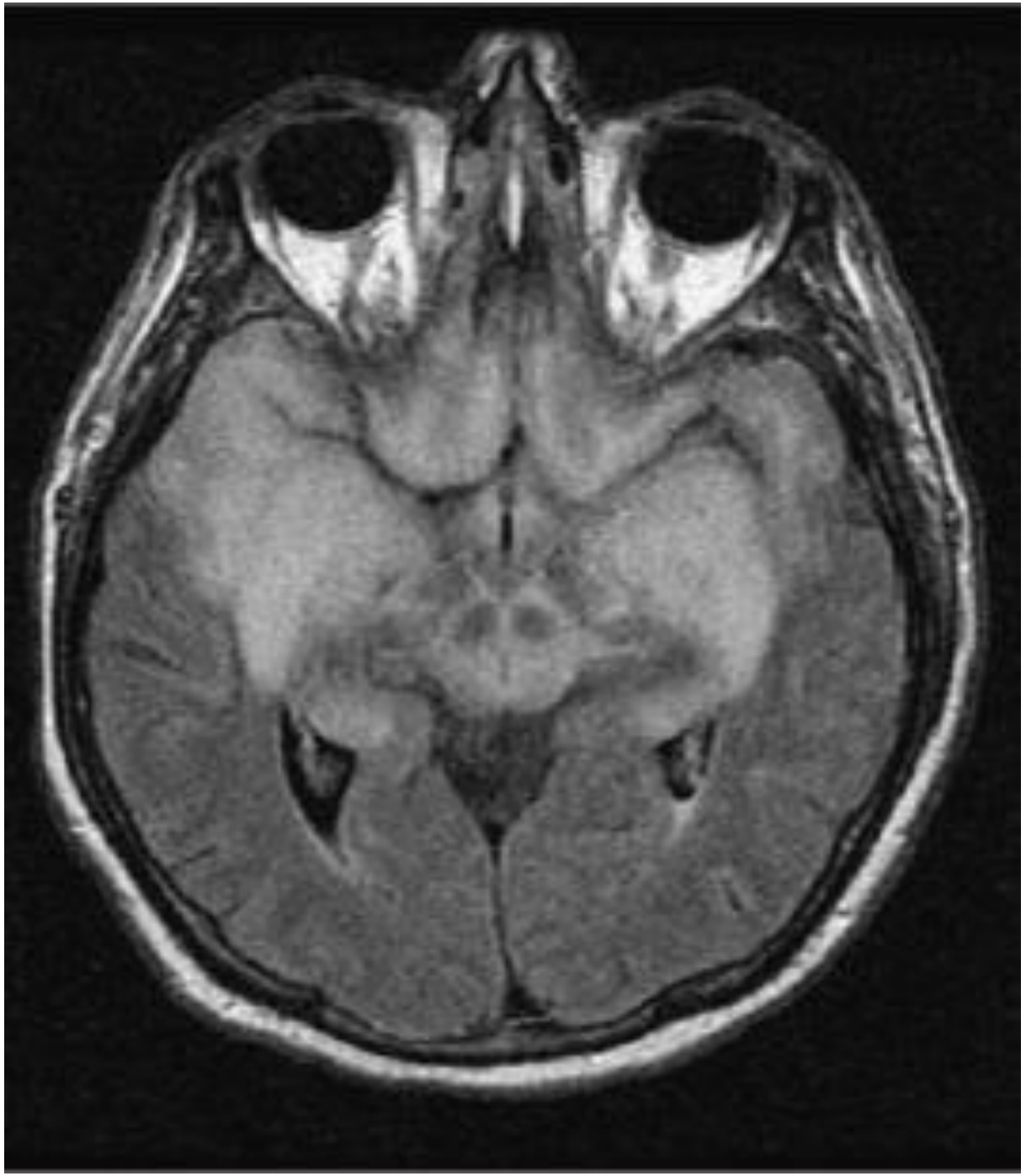
HD 5: Severe bradycardia requiring transvenous pacemaker placement.

HD 6: Diabetes insipidus.

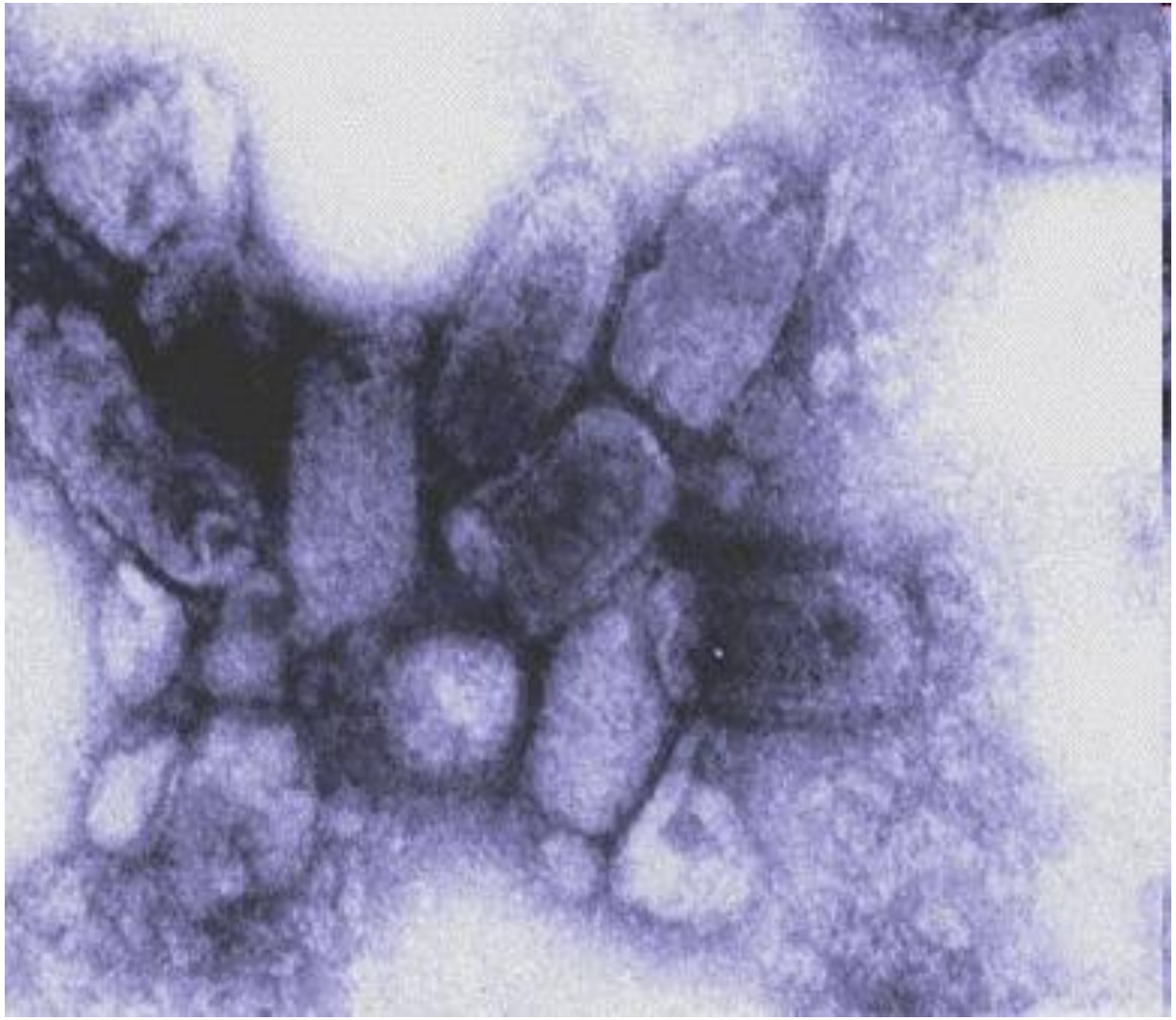
HD 7: Hypernatremia. Coagulopathy, anticoagulated for ECMO.

HD 8: Partial herniation from cerebral edema.

HD 12: Intracranial hemorrhage, patient expired.



Rabies Virus



Global Epidemiology

- 10 million people / year have potential exposure
- World Health Organization
  - Incidence - ~40-60,000 human cases
  - Fatalities - ~50,000 cases each year
- Majority of cases are in the developing world
  - Indian subcontinent with >30,000 cases/year
  - 35.5 deaths per 1 million people
  - 1596 autopsies in Columbia: 1.7% with undx rabies
  - ~75 Thai people die of rabies each year
- 4-10 million human post-exposure treatments annually
  - 5 million in China, 1 million in India, 40,000 in North America

Global Epidemiology

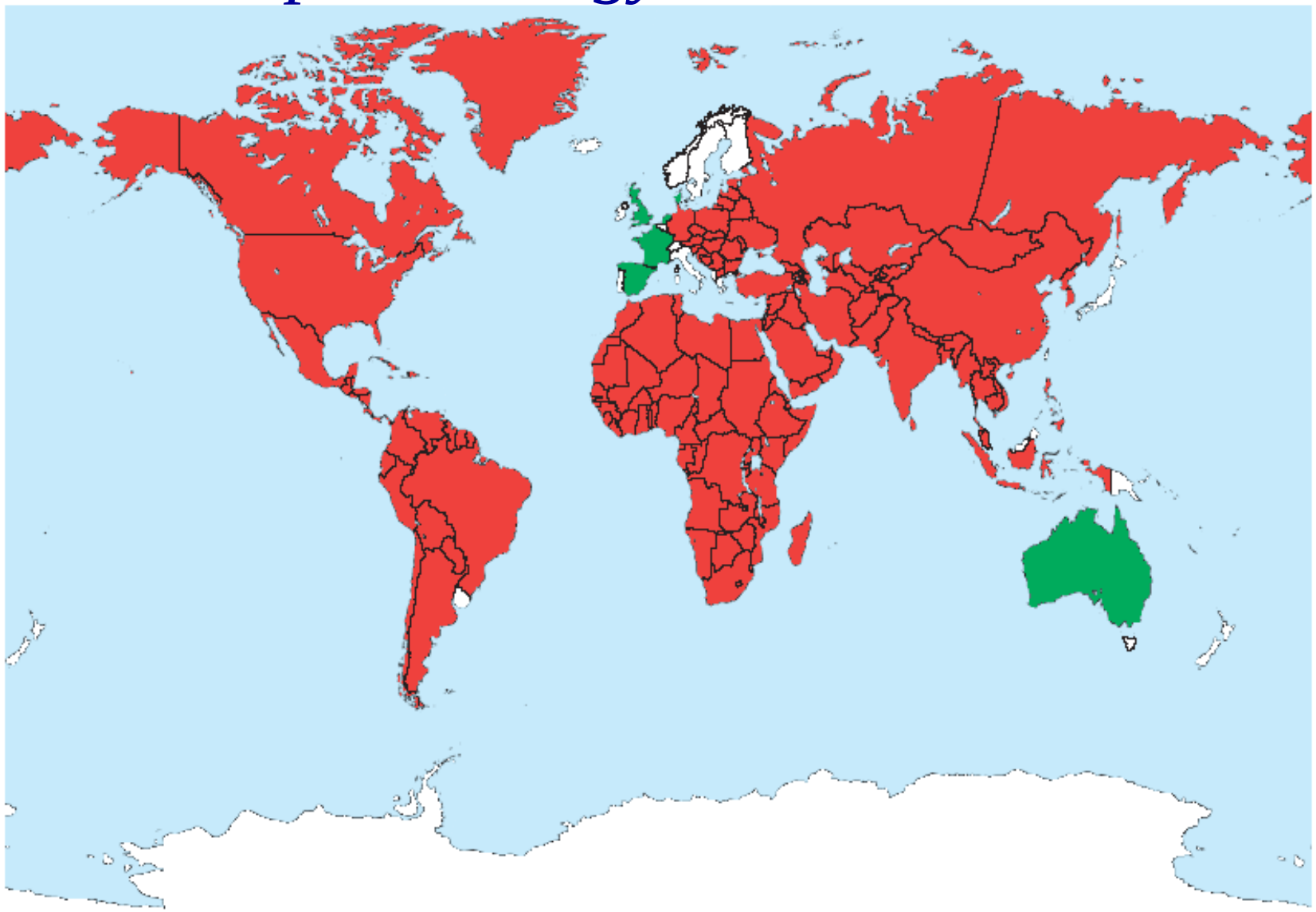
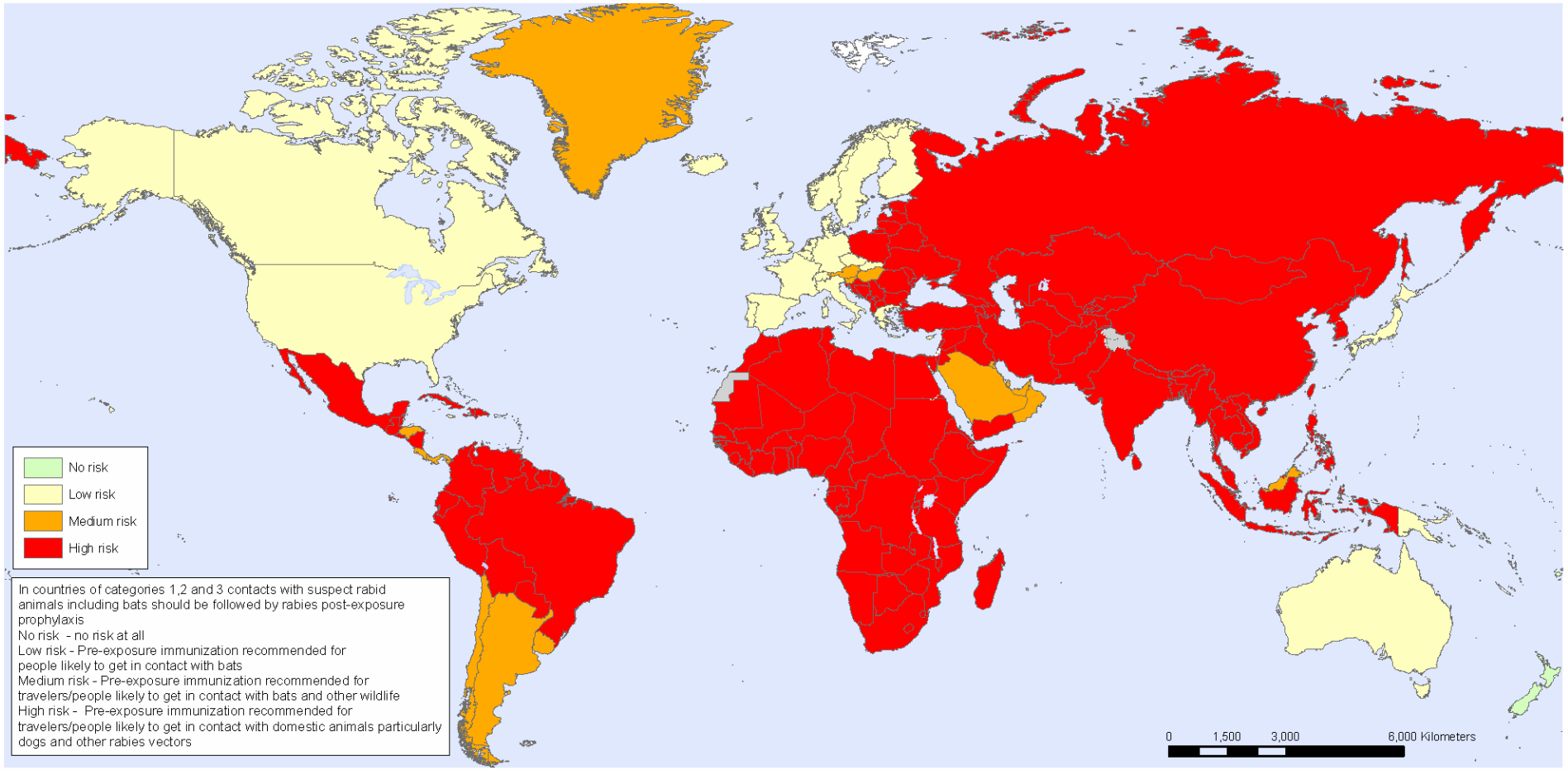


Figure 1: **Global distribution of lyssaviruses**
Distribution of rabies virus (red). Areas where rabies-related viruses only, not classic rabies genotype 1, are documented are classified by the WHO as "rabies-free" (green). White=rabies-free.

Rabies, countries or areas at risk



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Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Rabies in the Americas: 1993-2002

A. Belotto et al. / Virus Research 111 (2005) 5–12

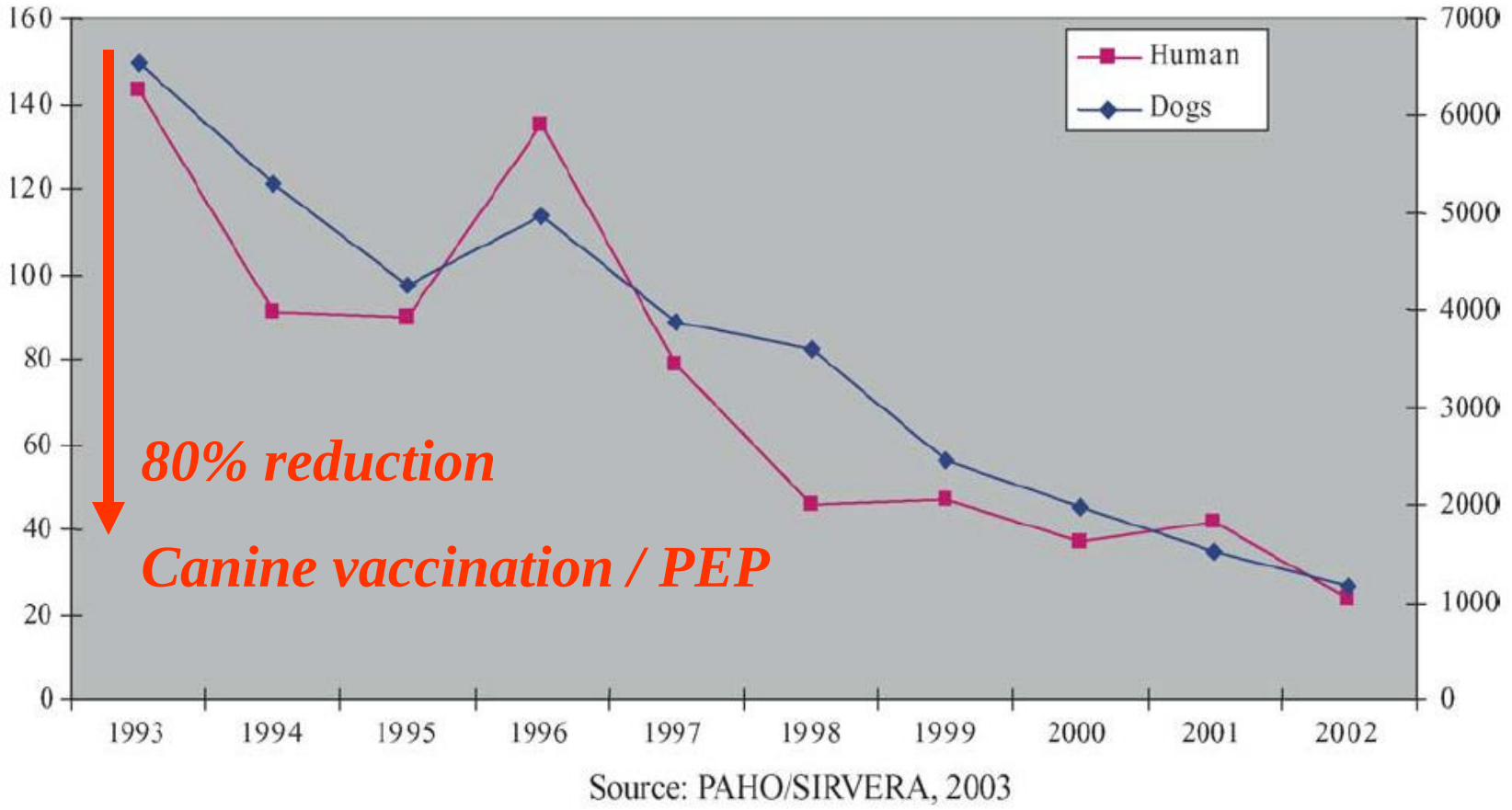
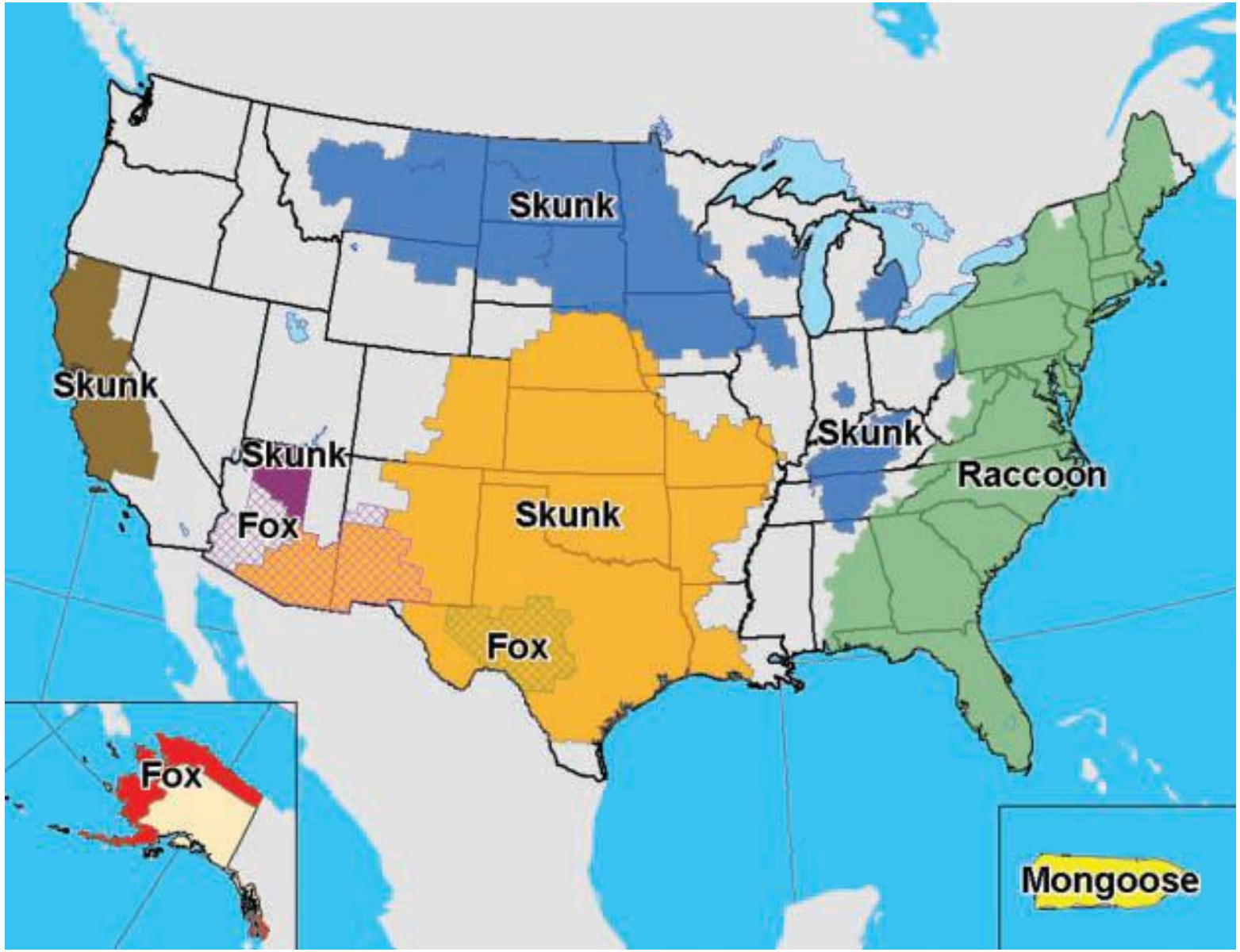


Fig. 1. Human rabies cases and rabies cases in dogs, Region of the Americas, 1993–2002 (source: PAHO/SIRVERA, 2003).

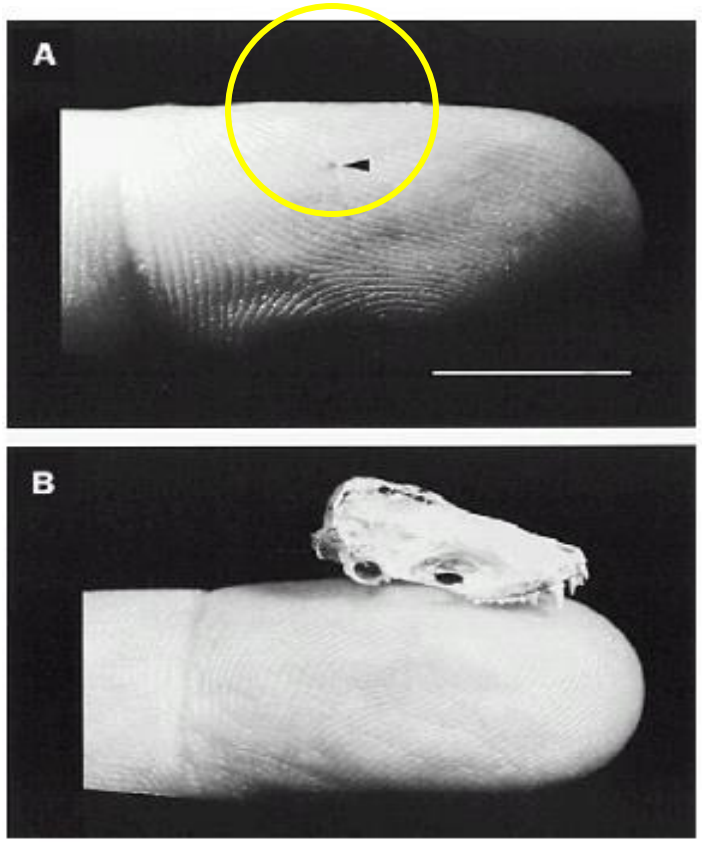
North American Epidemiology

- Average of 55 human cases/year between 1900-1950
- United States
  - 36 cases in the last 20 years.
  - 24/36 were believed acquired in the US.
  - 21/24 cases: domestic bat strain
  - 71% silver haired bat variant
  - 2/24 dog/coyote strain
  - 1/24 skunk strain

Distribution of rabies virus among animals in the United States and Puerto Rico, 2008.



Silver haired bat: – predominant rabies risk
–virus infects skin more readily
–small teeth with little evidence of bite



Puncture wound of a bite from a silver-haired bat (A, arrow) and skull of silver-haired bat (B)

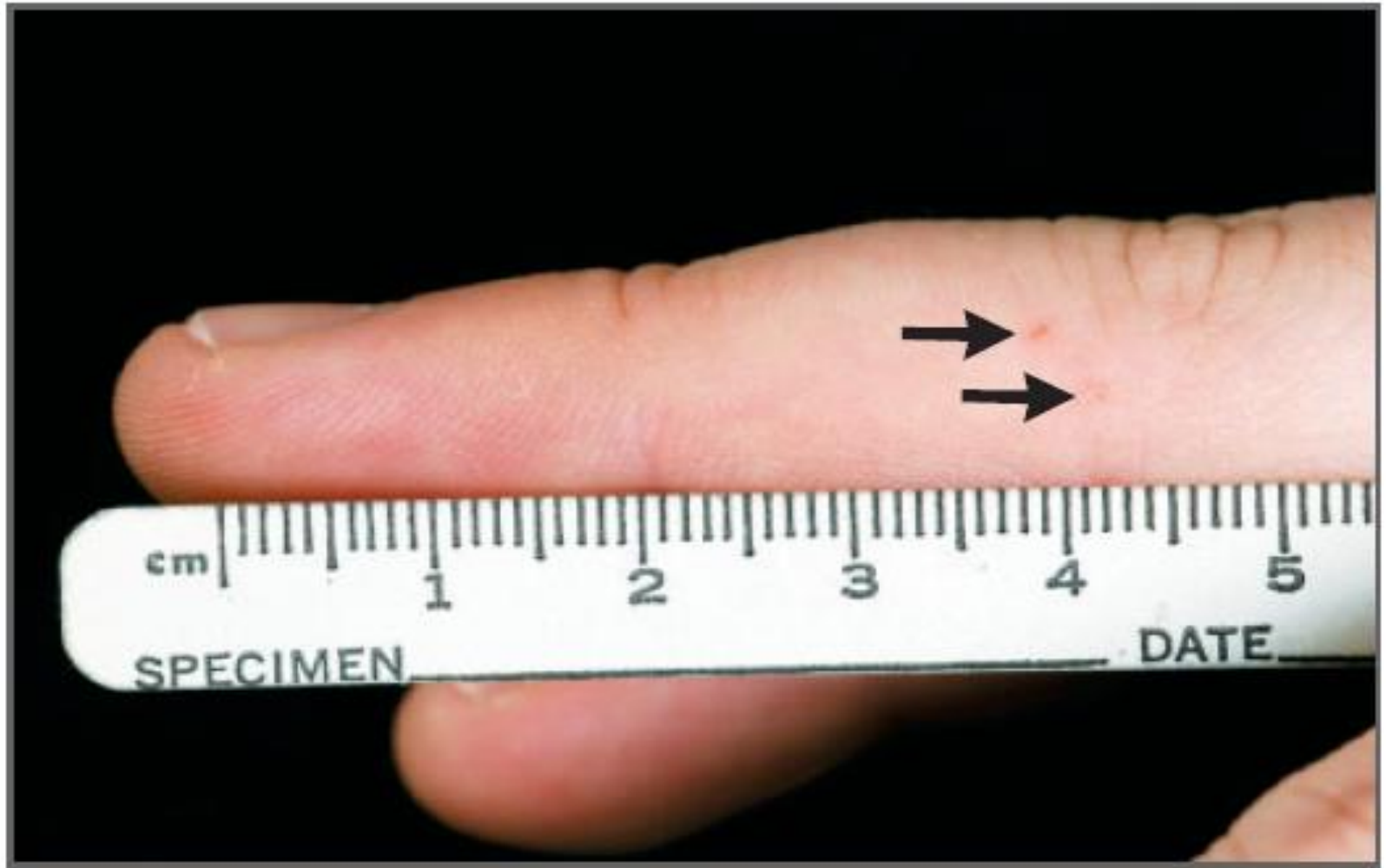
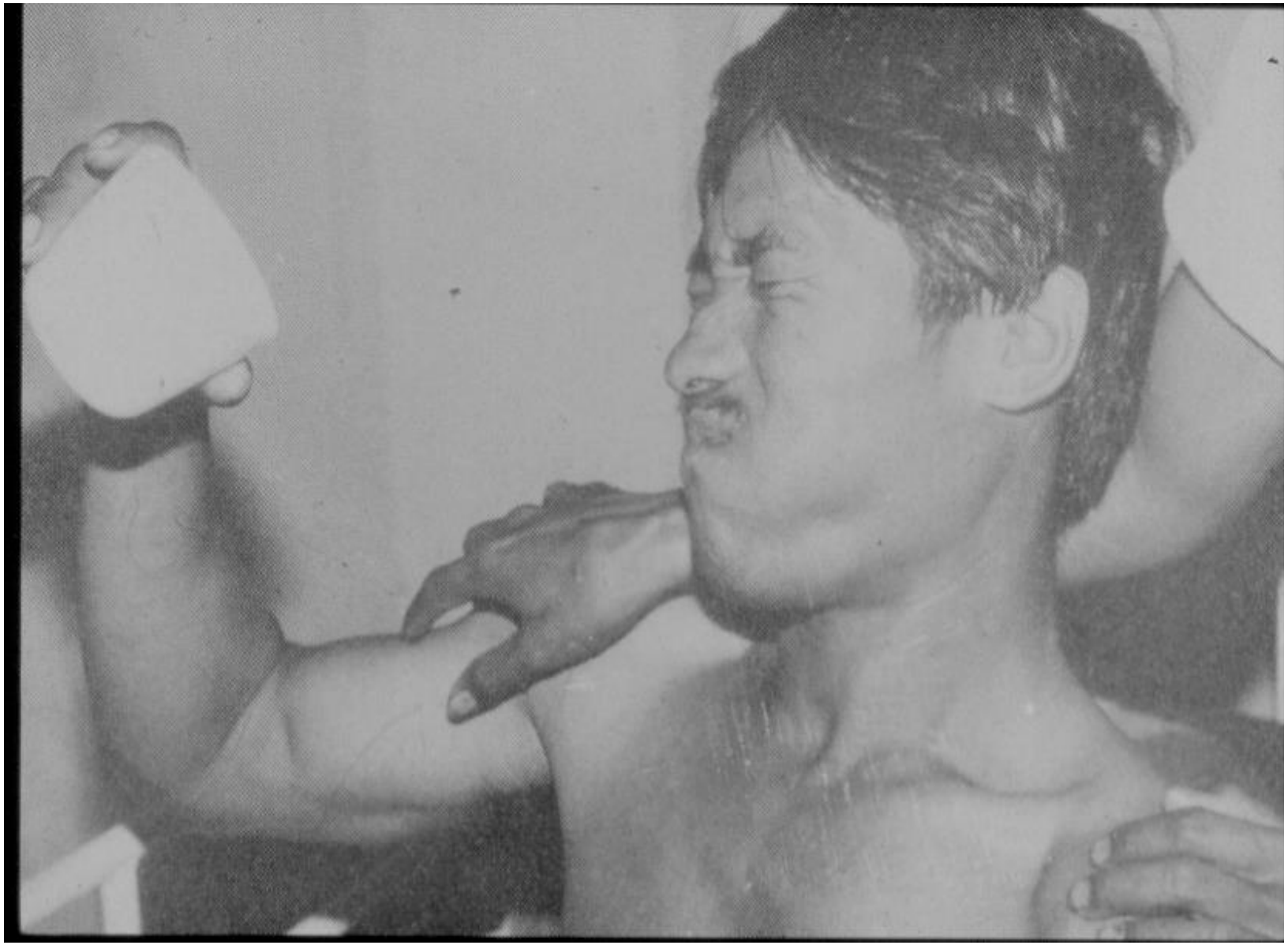


Figure 2. Bat Bite (Arrows) on the Finger.

The bite occurred in a 23-year-old man as he handled a bat.

Clinical Rabies

- Incubation period
  - 95% of cases < 1 year; 1-3% of cases, incubation >6 months; reported cases with incubation 7 – 19 years
- Prodromal period - 2 to 10 days
  - Symptoms
    - chills, fever, headache, photophobia, anorexia, nausea vomiting, diarrhea, sore throat, cough, malaise
  - Signs
    - Abnormal sensation around the bite site
      - Itching, burning, numbness, or paresthesia
    - Myoedema (prodromal period with persistence)
      - Mounding of part of the muscle struck with a reflex hammer



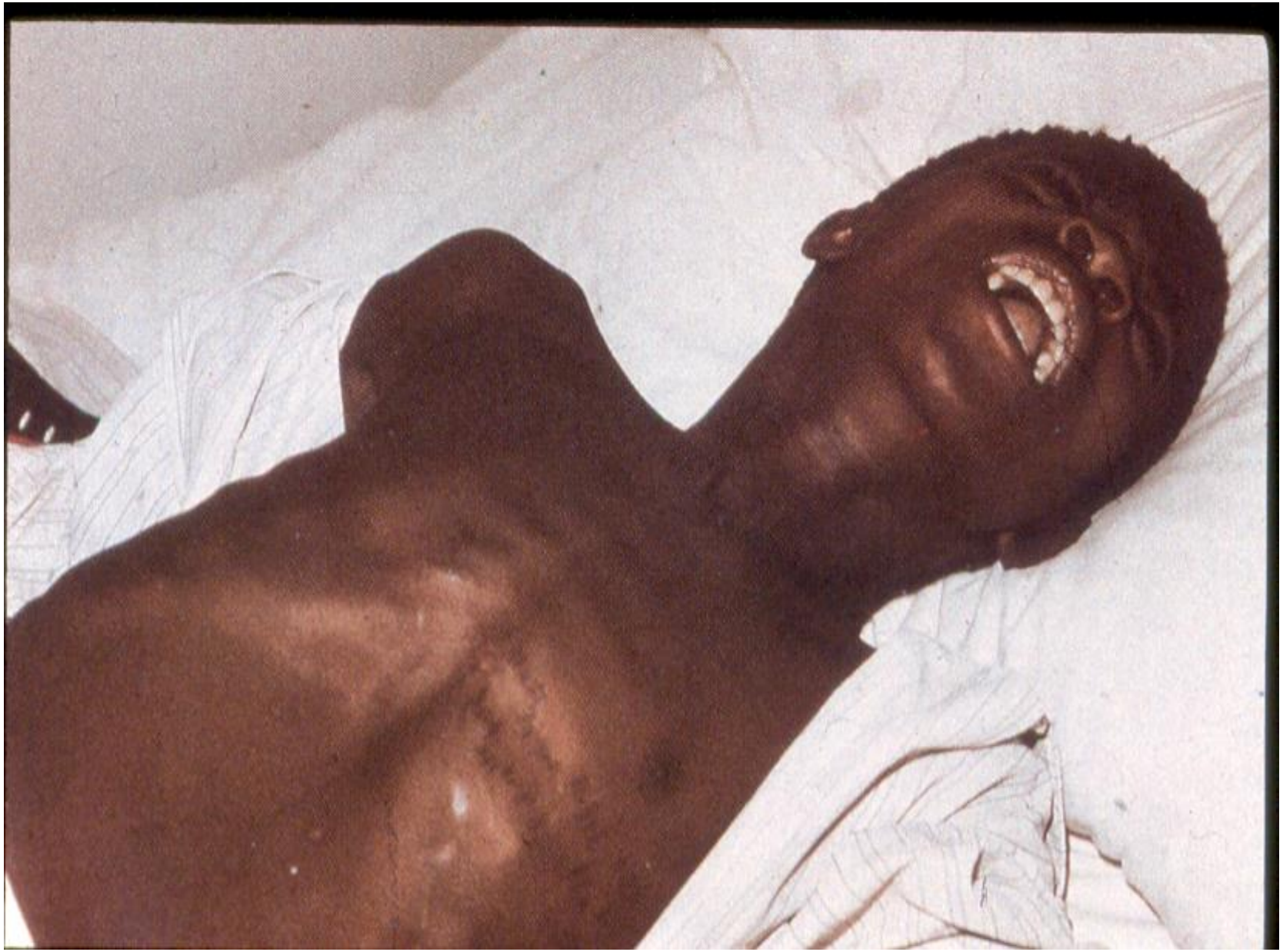
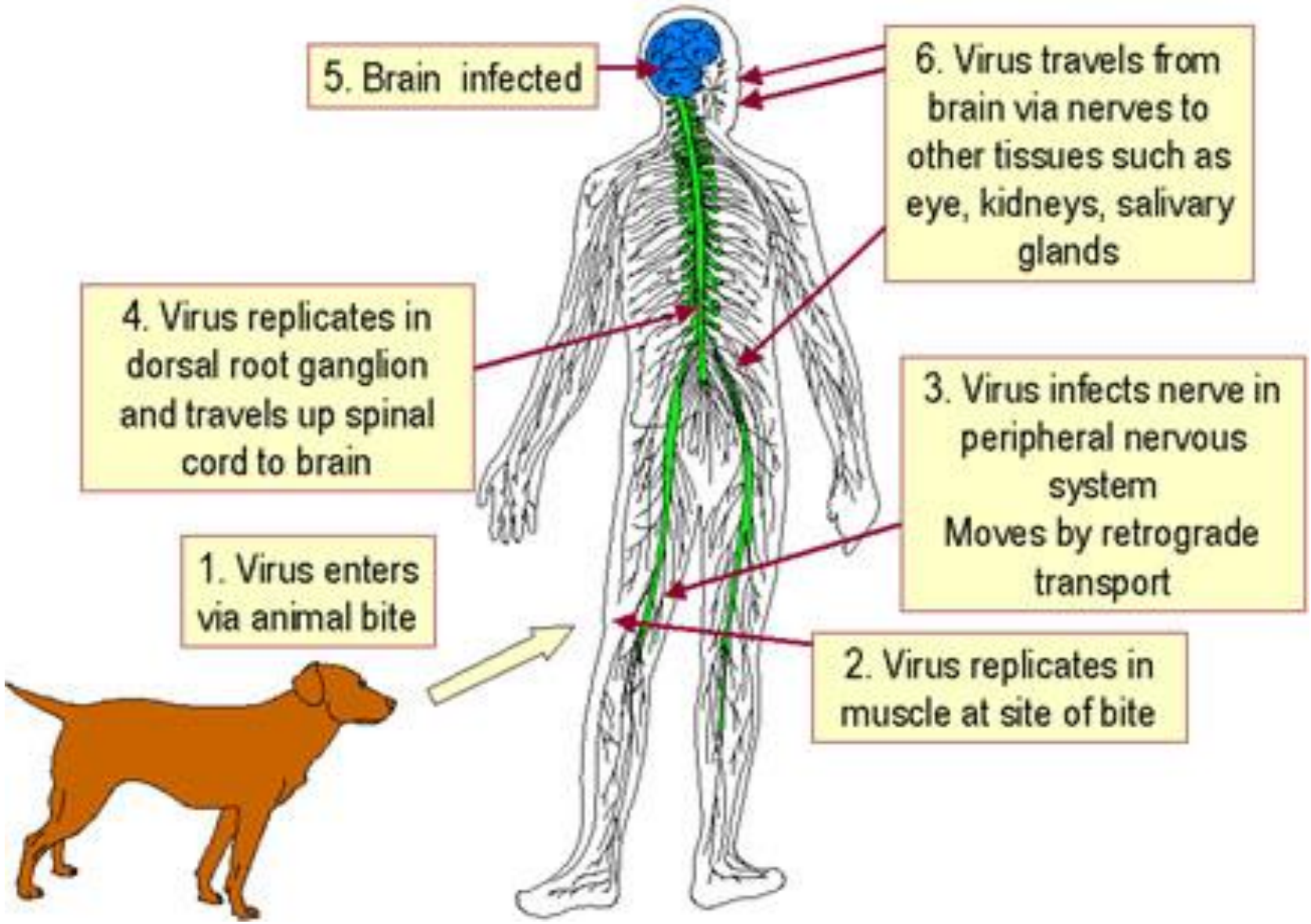


FIGURE 21–5. Sweating and hypersalivation in a Thai woman with furious rabies. (Copyright D. A. Warrell.)

Virulence

- Determinants of virulence
  - Location and severity of a bite
  - Species of animal responsible for the exposure
- Determinants of mortality
  - Head and face (40% to 80%),
  - Hands or arms (15% to 40%),
  - Trunk or legs (5% to 10%), or through clothing (<5%)
- Incubation period
  - Usually 1 to 2 months, varies, < than a week to many years


5. Brain infected
6. Virus travels from brain via nerves to other tissues such as eye, kidneys, salivary glands
4. Virus replicates in dorsal root ganglion and travels up spinal cord to brain
3. Virus infects nerve in peripheral nervous system
Moves by retrograde transport
1. Virus enters via animal bite
2. Virus replicates in muscle at site of bite

Protecting the Soldier

- Pre-exposure
  - Education (avoid animal bites, report immediately)
  - Rabies vaccine
- Post-exposure
  - Remove free virus from tissues
    - Irrigation with saline, debridement, cleaning with soap
    - Povidine solution increases efficacy
  - Induce a rabies virus-specific immune response
    - Passive antibody, rabies immune globlulin
    - Active immunization rabies vaccine

Multi-Drug Resistant Bacterial Infections

- *Acinetobacter baumannii-calcoaceticus* complex (ABC) organisms are gram-negative bacteria found in soil and water.
- They are an emerging cause of health care–associated outbreaks of infection, especially among critically ill and immunocompromised patients.

- In March 2003, soon after the beginning of the US Military's combat operations in Iraq known as Operation Iraqi Freedom (OIF), a marked increase was observed in the number of multidrug-resistant ABC infections among inpatients at Landstuhl Regional Medical Center (LRMC; Landstuhl, Germany) and at Walter Reed Army Medical Center (WRAMC;Washington, DC).
- Most injured service members were initially treated at these 2 facilities after evacuation from Iraq. Many of these infections were detected at or soon after hospital admission to LRMC or WRAMC, but the source of the infections was not apparent.

Figure 1. Aeromedical evacuation route from Iraq and Kuwait to US Military hospitals in Europe and the United States. LRMC, Landstuhl Regional Medical Center; USNS, US Naval Ship; WRAMC, Walter Reed Army Medical Center

Combat Support Hospital

Contributing Factors

- Rapid evacuation with increase survival from severe trauma.
- Dirty wounds from improvised explosive devices (IEDs).
- Use of antibiotics for prophylaxis.

Conclusions of Investigation

- Environmental contamination of field hospitals and infection transmission within health care facilities played a major role in this outbreak.
- Maintaining infection control throughout the military health care system is essential.
- Novel strategies may be required to prevent the transmission of pathogens in combat field hospitals.

Deployment of Marines to Monrovia

- In August 2003, 225 Marines with the 26th Marine Expeditionary Unit aboard U.S. Navy ships were deployed to Roberts International Airport outside the coastal city of Monrovia.
- Liberia has a tropical climate that includes frequent rainstorms (average rain fall is 78 cm/month) and daytime high temperatures average approximately 27°C in the summer months.
- Years of conflict and lack of a functioning government has led to the neglect of disease and vector control programs. As a result, Liberia is holoendemic for malaria.
- Deployed Marines worked and slept in an abandoned airport warehouse that had standing water and was infested with rats and mosquitoes. They had already been at sea for several months, most serving briefly in Iraq (April) and Djibouti (July) before arriving in Liberia in August.

- For malaria chemoprophylaxis during deployment, Marines were issued a supply of generic mefloquine (MQ) hydrochloride (250 mg tablets; Geneva Pharmaceuticals, Dayton, NJ), which were foil-wrapped in blister packs. Each Marine was given several blister packs before going ashore in the Middle East and Africa.
- Adherence with weekly MQ was based on the honor system, not directly observed therapy (DOT). None of the Marines used doxycycline or atovaquone/proguanil as chemoprophylaxis.
- The unit spent 10 days in Liberia. Within one day after returning to their ships, a febrile illness developed in the first of what amounted to 80 Marines.

FIGURE 1. Warehouse that housed U.S. Marines at Roberts Interactional Airport in Monrovia, Liberia demonstrating numerous risk factors for contracting an arthropod-borne illness including broken windows, persons sleeping on the roof, standing water, and tall grass in the surrounding area, for contracting an arthropod-borne illness. This figure appears in color at www.ajtmh.org.

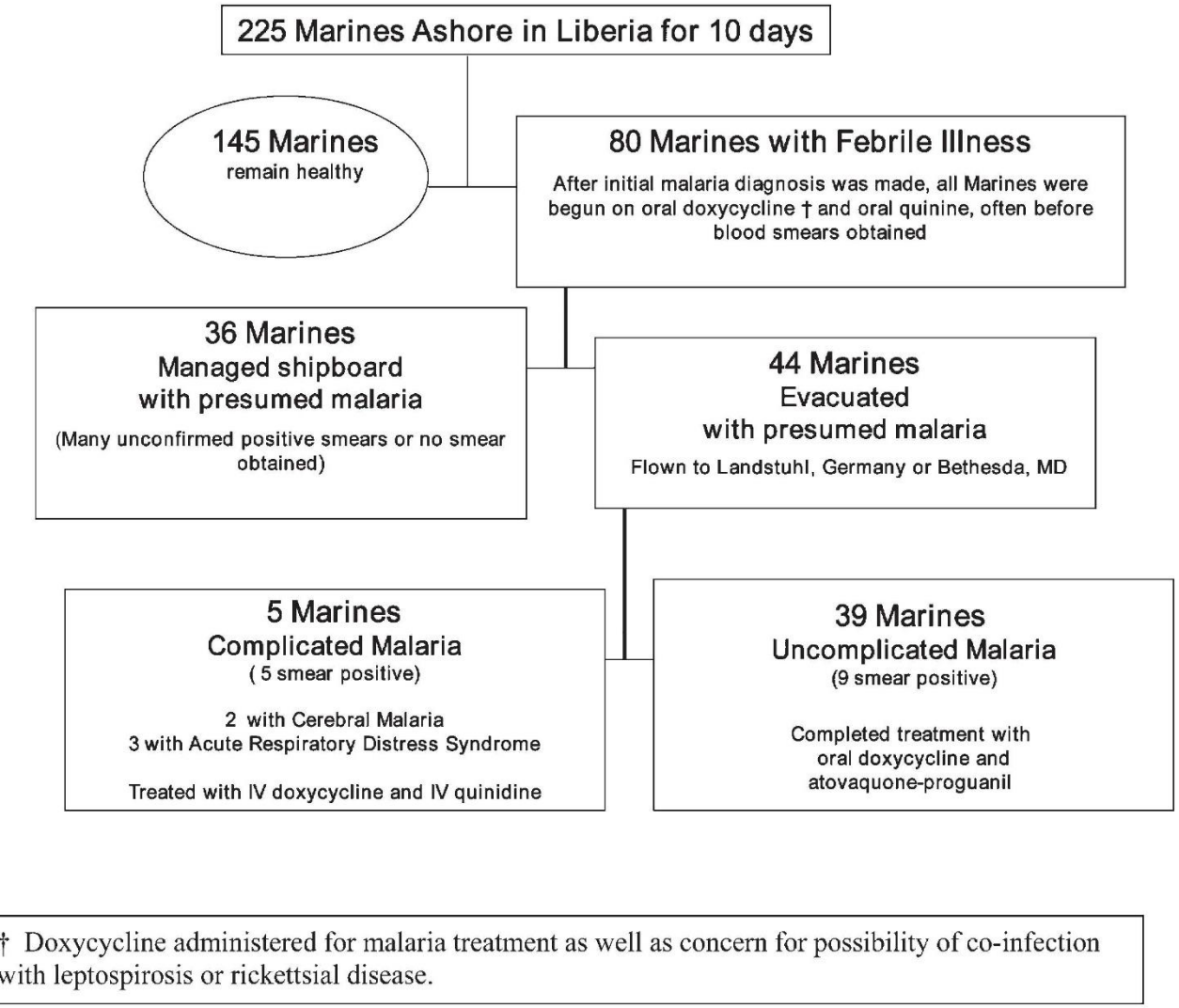


FIGURE 2. Flow diagram of U.S. Marines ashore in Liberia. † Doxycycline administered for malaria treatment and for possible co-infection with leptospirosis or rickettsial disease.

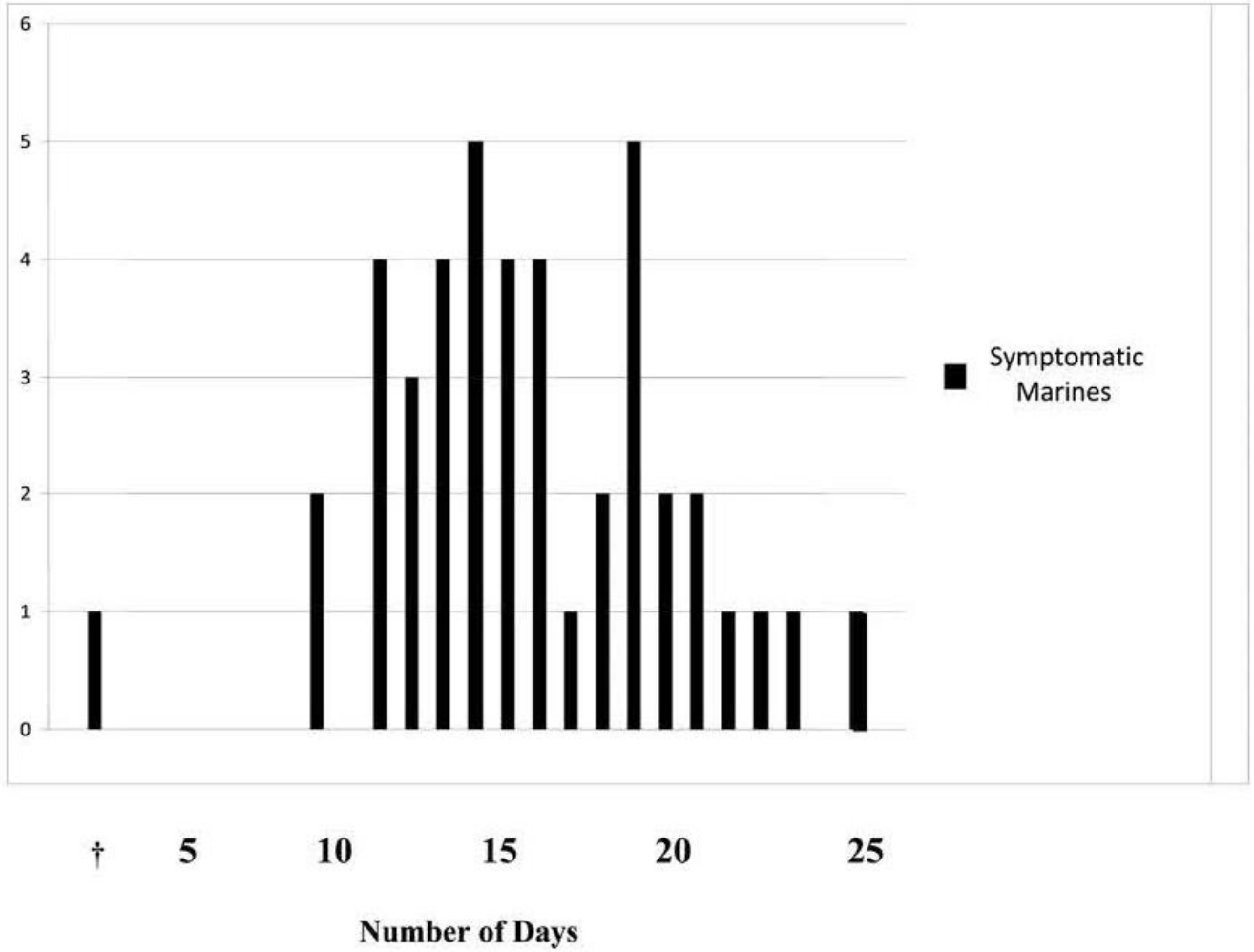
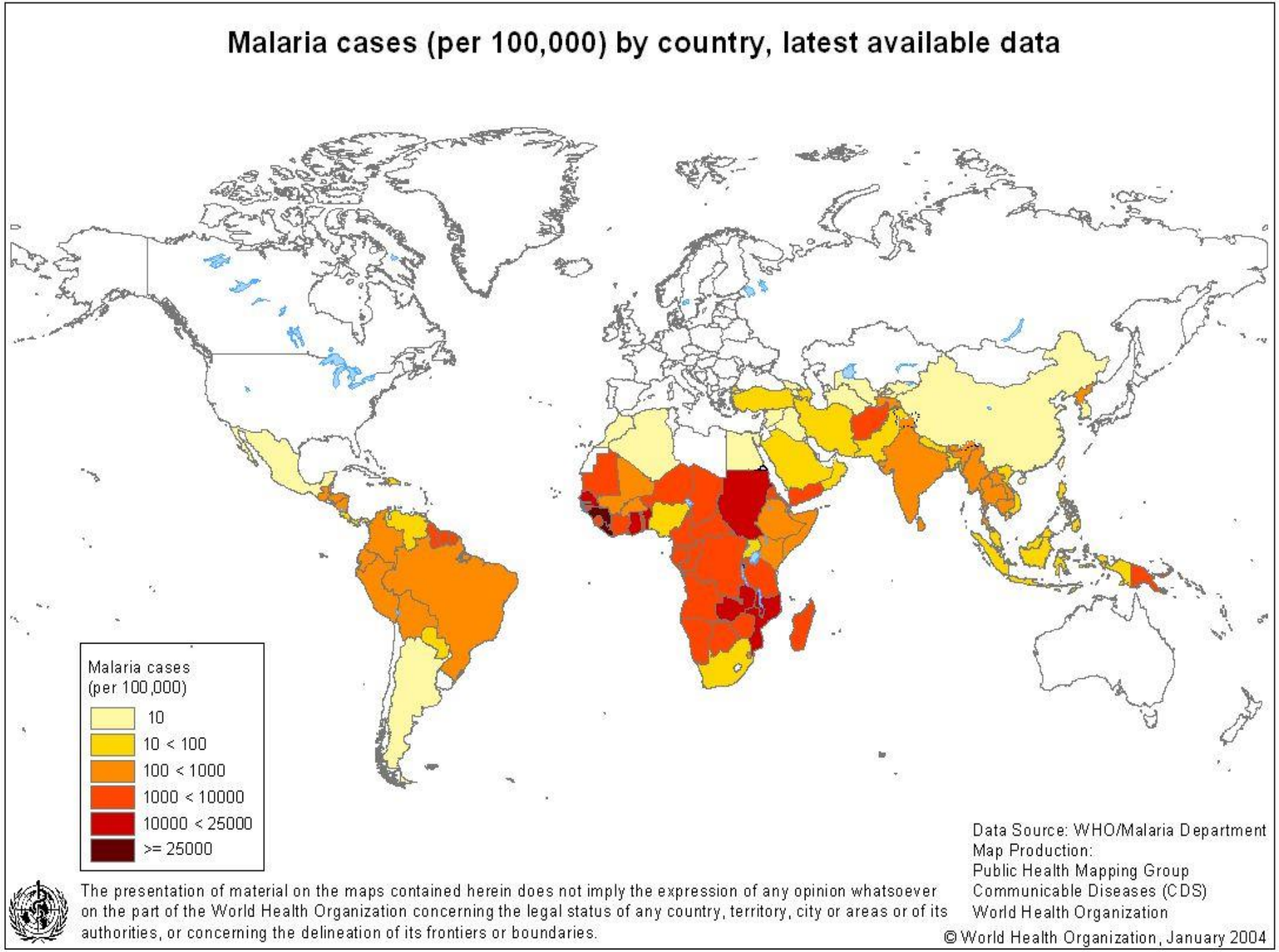


FIGURE 3. Epidemic curve showing the onset of symptoms in days after first possible exposure in Liberia. † The symptoms this U.S. Marine reported on day 1 in Liberia were not considered related to malaria.


Malaria cases (per 100,000) by country, latest available data
Malaria cases
(per 100,000)
10
10 < 100
100 < 1000
1000 < 10000
10000 < 25000
>= 25000
Data Source: WHO/Malaria Department
Map Production:
Public Health Mapping Group
Communicable Diseases (CDS)
World Health Organization
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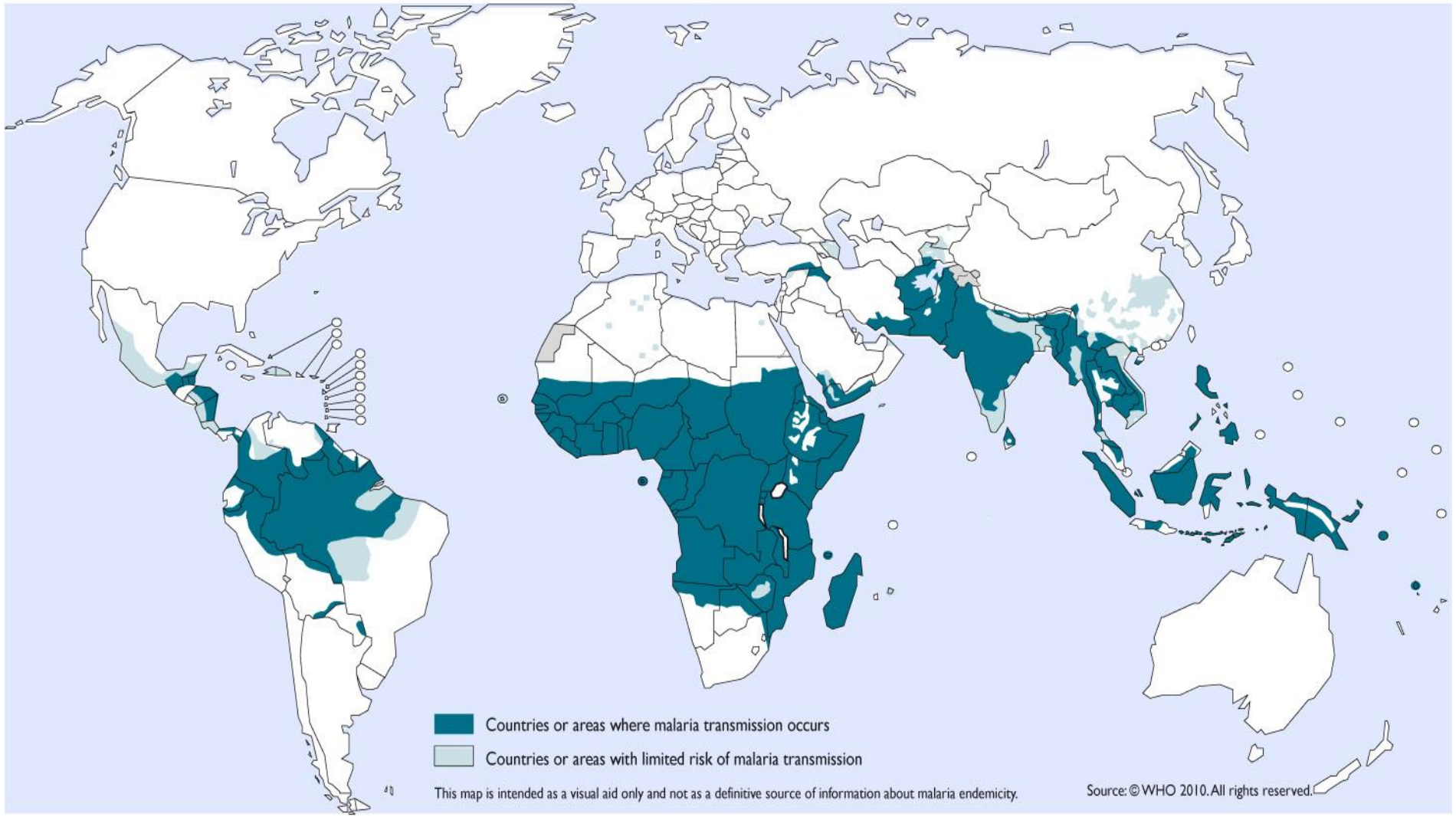
Malaria, countries or areas at risk of transmission, 2009



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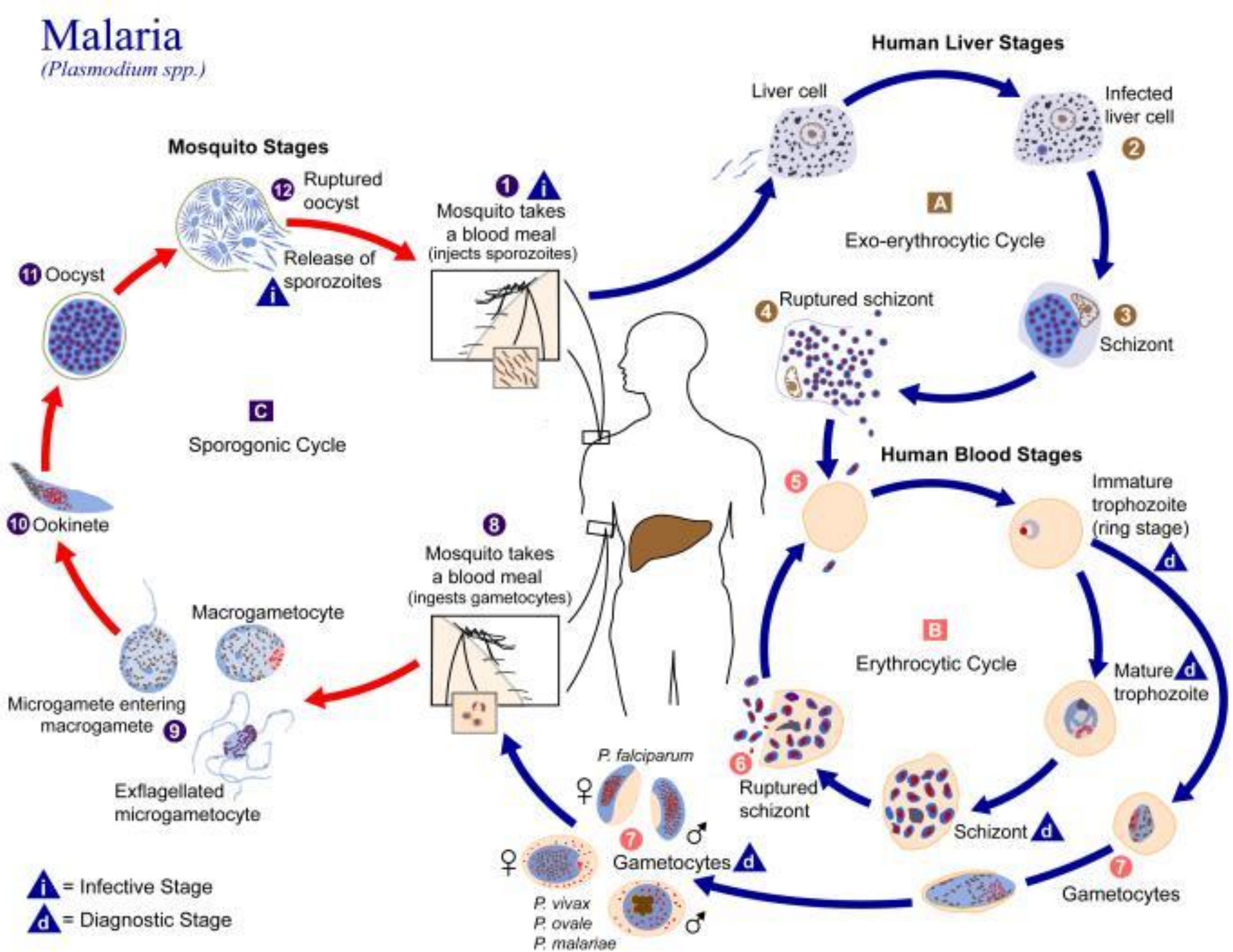
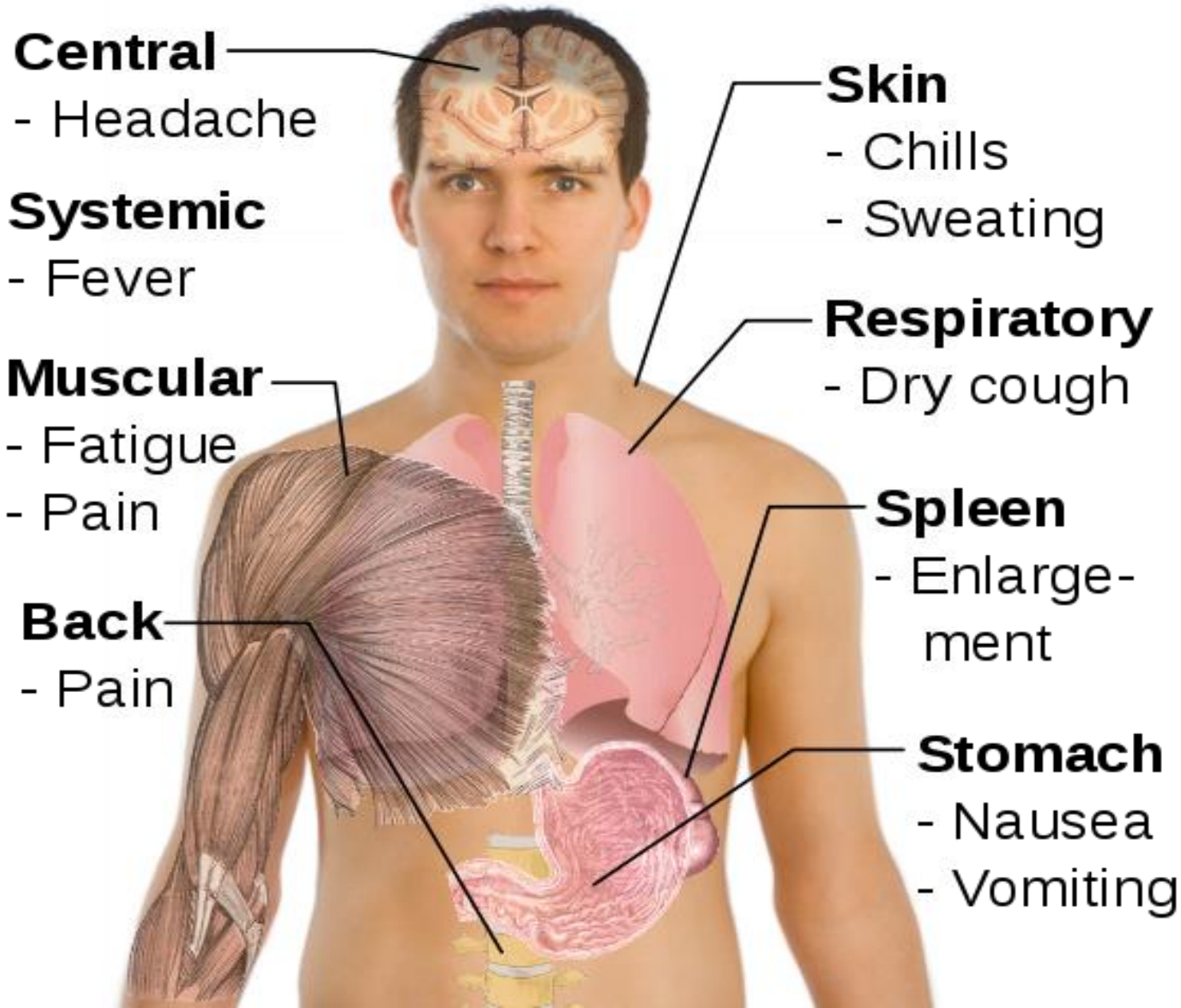
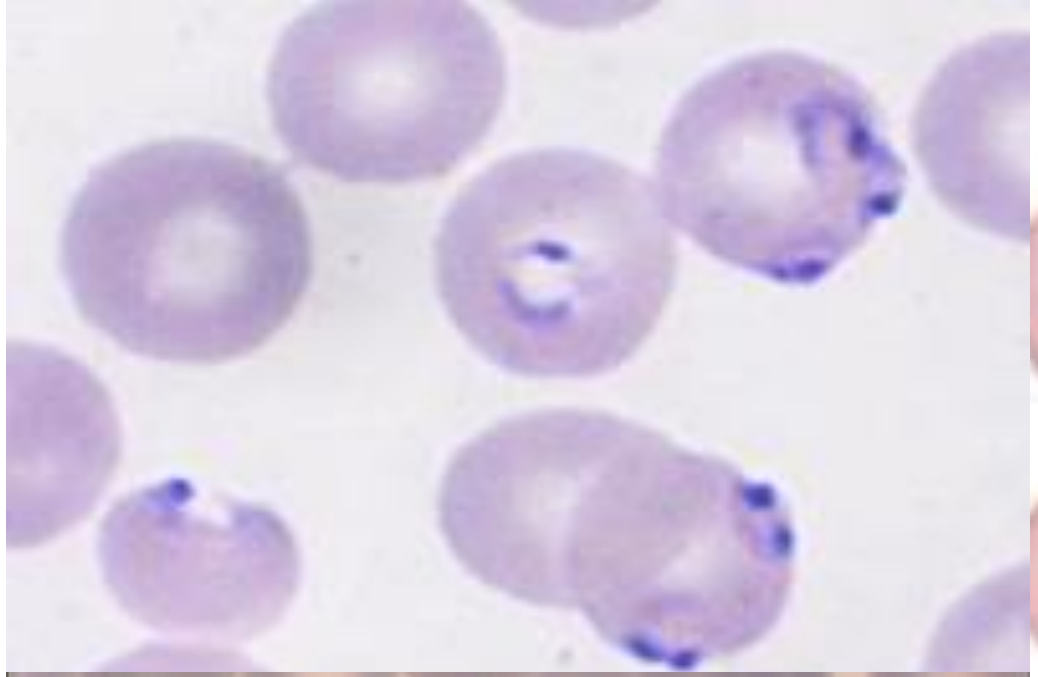
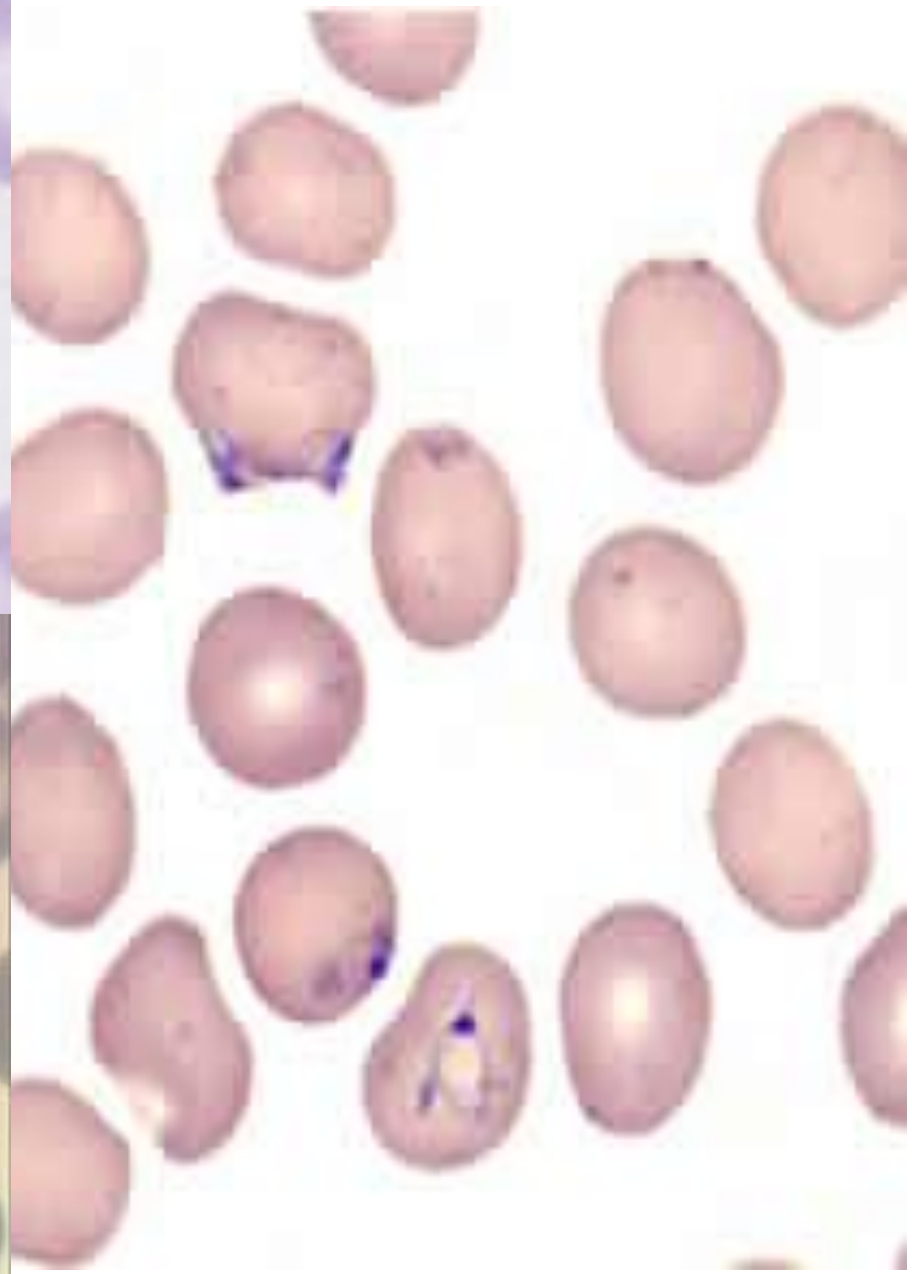

Malaria
(Plasmodium spp.)
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
Ruptured schizont
4
3
Schizont
Mosquito Stages
12
Ruptured oocyst
1
i
Mosquito takes a blood meal
(injects sporozoites)
Release of sporozoites
i
11 Oocyst
C
Sporogonic Cycle
Human Blood Stages
5
Immature trophozoite (ring stage)
d
10 Ookinete
8
Mosquito takes a blood meal
(ingests gametocytes)
Macrogametocyte
B
Erythrocytic Cycle
Mature trophozoite
d
Microgamete entering macrogamete
9
Exflagellated microgametocyte
P. falciparum
6
Ruptured schizont
Schizont
d
7
Gametocytes
d
7
Gametocytes
P. vivax
P. ovale
P. malariae
i = Infective Stage
d = Diagnostic Stage

Symptoms of

Malaria







Uncomplicated Malaria

- Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

Complicated Malaria

- Patients who have one or more of the following:
  - impaired consciousness/coma
  - severe normocytic anemia [hemoglobin < 7]
  - renal failure
  - acute respiratory distress syndrome
  - hypotension
  - disseminated intravascular coagulation
  - spontaneous bleeding
  - acidosis
  - hemoglobinuria
  - jaundice
  - repeated generalized convulsions
  - and/or parasitemia of > 5%

Protecting Soldiers

- Bednets
- Education
- Mandatory observed malaria prophylaxis

Malaria Prophylaxis

Table 1. **Drug Regimens for Prophylaxis against Malaria.***

Drug	Tablet Size	Adult Dose	Use in Children†	Use in Pregnancy	Initiation (Time before First Exposure to Malaria)	Discontinuation (Time after Last Exposure)	Advantages	Disadvantages
Areas with chloroquine-resistant *Plasmodium falciparum*								
Atovaquone–proguanil (Malarone)	Adult: 250 mg of atovaquone and 100 mg of proguanil once daily; pediatric: 62.5 mg of atovaquone and 25.0 mg of proguanil	250 mg and 100 mg once daily	Yes; FDA-approved for children ≥11 kg (in children 5 to <11 kg, recommended off-label use by CDC)	No; insufficient data on use in pregnancy, not recommended by CDC	1–2 days	7 days	Short courses for brief trips; best-tolerated antimalarial agent; discontinuation rates of 0–1.2% in randomized clinical trials	Expensive; cost may be prohibitive for long trips; contraindicated if creatinine clearance <30 ml/min; must be taken with food
Mefloquine hydrochloride (Lariam and generic agents)	250 mg (228-mg mefloquine base)‡	250 mg once weekly	Yes; approved for children ≥5 kg (in children <5 kg, recommended off-label use by CDC)	Yes; limited data available on first-trimester use	3 wk preferable; 1–2 wk acceptable	4 wk	Most convenient antimalarial agent for long trips; long experience with prolonged use	Mefloquine resistance in remote areas of Southeast Asia; contraindicated in persons with active or recent depression, history of psychosis, seizure disorder, AV-node conduction abnormalities; adverse events include vivid dreams or nightmares, insomnia, mood alteration, first-degree AV block, prolonged QT interval, and seizures (rare); approximately 5% rate of premature discontinuation; well tolerated by most travelers; extra counseling required because of adverse publicity
Doxycycline hyclate (Vibramycin, Vibra-Tabs, other brands, and generic agents); doxycycline monohydrate (Monodox, Adoxa, and generic agents)	Doxycycline hyclate: 20 mg, 50 mg, or 100 mg; doxycycline monohydrate: 100 mg	100 mg once daily	Contraindicated for children <8 yr old because of staining of dental enamel	No; teratogenic	1–2 days	4 wk	Inexpensive; widely available worldwide	Photosensitivity (particular concern in tropical sun); gastritis and esophagitis; must be taken on full stomach with glass of liquid, and traveler must remain in upright position for 30 min; candidal infections, including vaginitis in humid tropical climates; risk of vaginal yeast infection (women travelers should take along medication for self-administered treatment); approximately 5% rate of premature discontinuation
Areas with chloroquine-sensitive *P. falciparum*								
Chloroquine phosphate (Aralen and generic agents)	500 mg (300-mg chloroquine base); some generic agents available in 250-mg (150-mg base) tablet	500 mg once weekly	Yes; approved for all ages	Yes	1 wk	4 wk	60-yr record of safety	Useful in very limited geographic areas; pruritus in dark-skinned persons; rare blood dyscrasias; cannot use if traveler has psoriasis, history of psychosis, or prolonged QT interval; rare retinopathy (with >100-g total dose)
Areas with *P. vivax* and *P. ovale*, with or without *P. falciparum*								
Primaquine phosphate for primary prophylaxis (off-label use; second-line agent for this purpose)	26.3 mg (15-mg primaquine base)	30-mg base once daily	Yes; approved for all ages	No; contraindicated because of potential toxic effects on fetal erythrocytes	1 day	7 days	Short courses for brief trips; protection against primary clinical episode as well as late relapses due to *P. vivax* or *P. ovale*	G6PD testing required before first dose; contraindicated in travelers with G6PD deficiency due to hemolysis; must be taken with a meal to prevent gastric irritation; methemoglobinemia
Primaquine phosphate for relapse prevention (presumptive antirelapse therapy)	26.3 mg (15-mg primaquine base)	30-mg base once daily	Yes; approved for all ages	No	As soon as possible after exposure for which another prophylactic drug taken	Total of 14 days	Protection against late relapses when another agent taken for primary prophylaxis	G6PD testing required before first dose; contraindicated in travelers with G6PD deficiency; must be taken with a meal; use of second drug after the trip, with different regimen and different adverse-effect profile, can be complex; incomplete global data on risk of *P. vivax* and *P. ovale*; methemoglobinemia

* AV denotes atrioventricular, CDC Centers for Disease Control and Prevention, FDA Food and Drug Administration, and G6PD glucose-6-phosphate dehydrogenase.
† See Wilder-Smith[9] and Arguin et al.[5] for doses.
‡ In some countries, 250-mg tablets of Lariam contain 250 mg of mefloquine base, equivalent to 274 mg of mefloquine hydrochloride.

Lessons Learned

- Infections during deployment will continue to be a cause of non-combat illnesses and troop readiness.
- Understanding infectious disease threats should be a priority in planning of any military action.
- Education of the soldier and their leadership on prophylactic measures should be a priority.
- Prophylaxis when available should be mandatory.