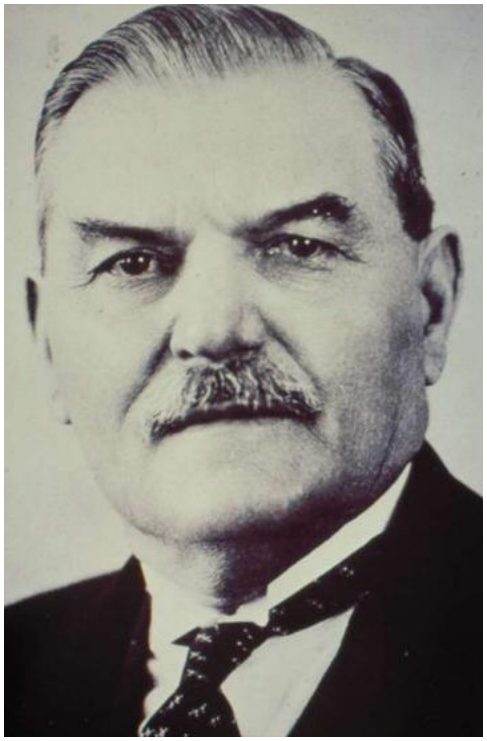
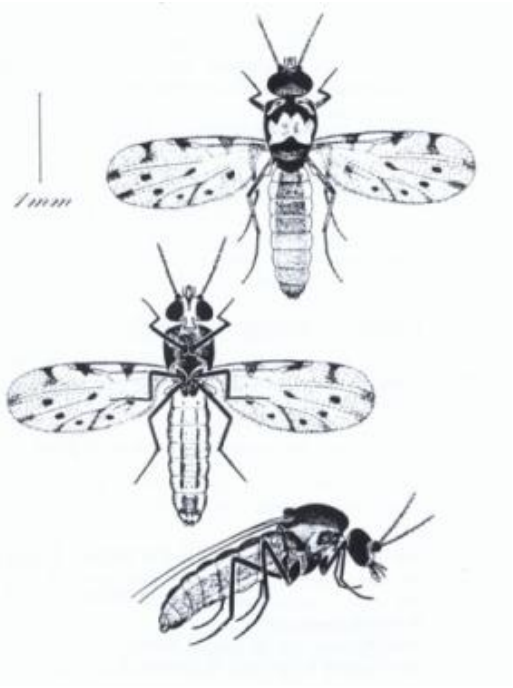
Emerging Viral Diseases; the Example of Bluetongue, from Theiler to Climate Change





Albrecht Dürer (circa 1498); Four Horsemen of the Apocalypse

And there, as I looked, was a fourth horse, sickly pale and its rider's name was Death, and Hades came close behind. To him was given power over a quarter of the Earth, to kill by sword and by famine and by pestilence and by wild beasts. (Revelation 6:1-8)

NEW, EMERGING AND RE-EMERGING DISEASES

- New & emerging diseases often = zoonoses e.g. West Nile, SARS, Henipah viruses, etc
  - Many = insect transmitted (vector-borne) from wildlife

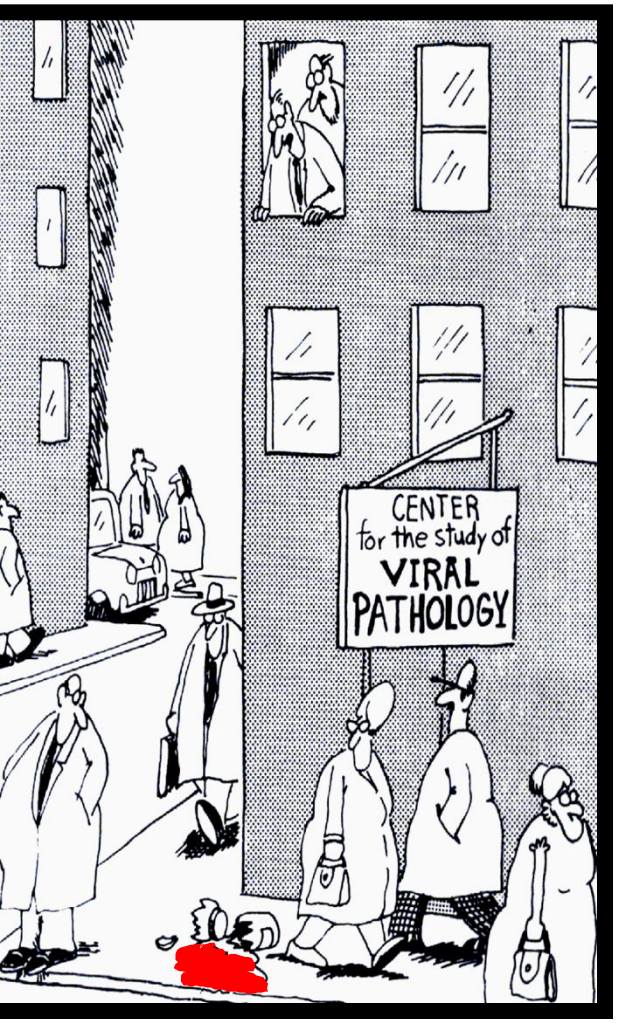
- Re-emerging = change in distribution of known pathogen, e.g.
  - Drug-resistant TB and malaria
  - Dengue and Yellow Fever from reduced use of insecticides, urban encroachment, etc

- Non-zoonotic livestock diseases can also be catastrophic to human societies e.g. Rinderpest

Rinderpest (Cattle Plague)

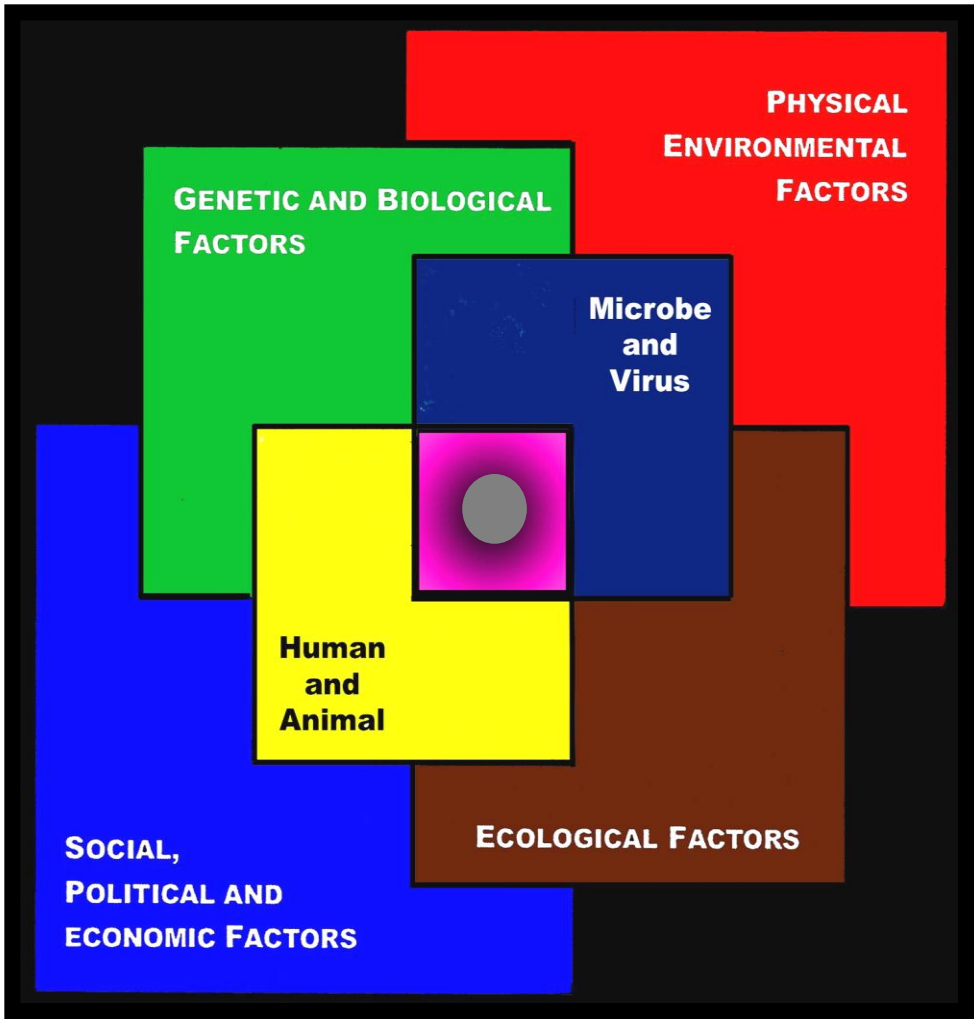
- **The historical impact of rinderpest was explained in graphic terms by Drs Gordon Scott and Alain Provost (1992) as: '*the most dreaded bovine plague known, belongs to a select group of notorious infectious diseases that have changed the course of history. From its homeland around the Caspian Basin rinderpest, century after century, swept west over and around Europe and east over and around Asia with every marauding army causing the disaster, death and devastation that preceded the fall of the Roman Empire, the conquest of Christian Europe by Charlemagne, the French Revolution, the impoverishment of Russia and the colonization of Africa.*"**

The Emergence of Viral Diseases: Perception versus Reality!



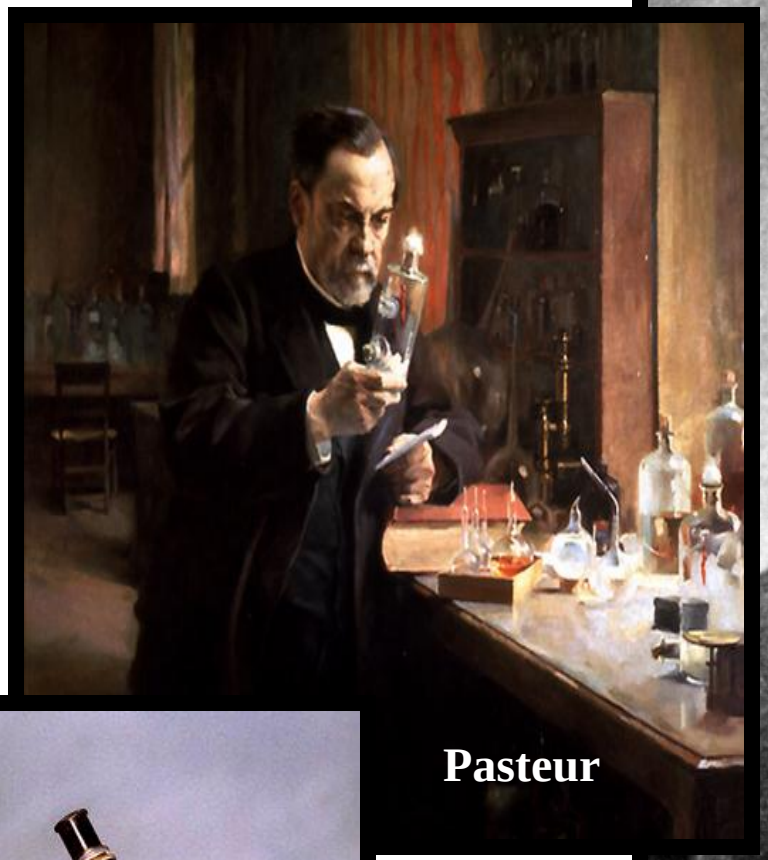
Uh-Oh!

The Far Side, By Gary Larson

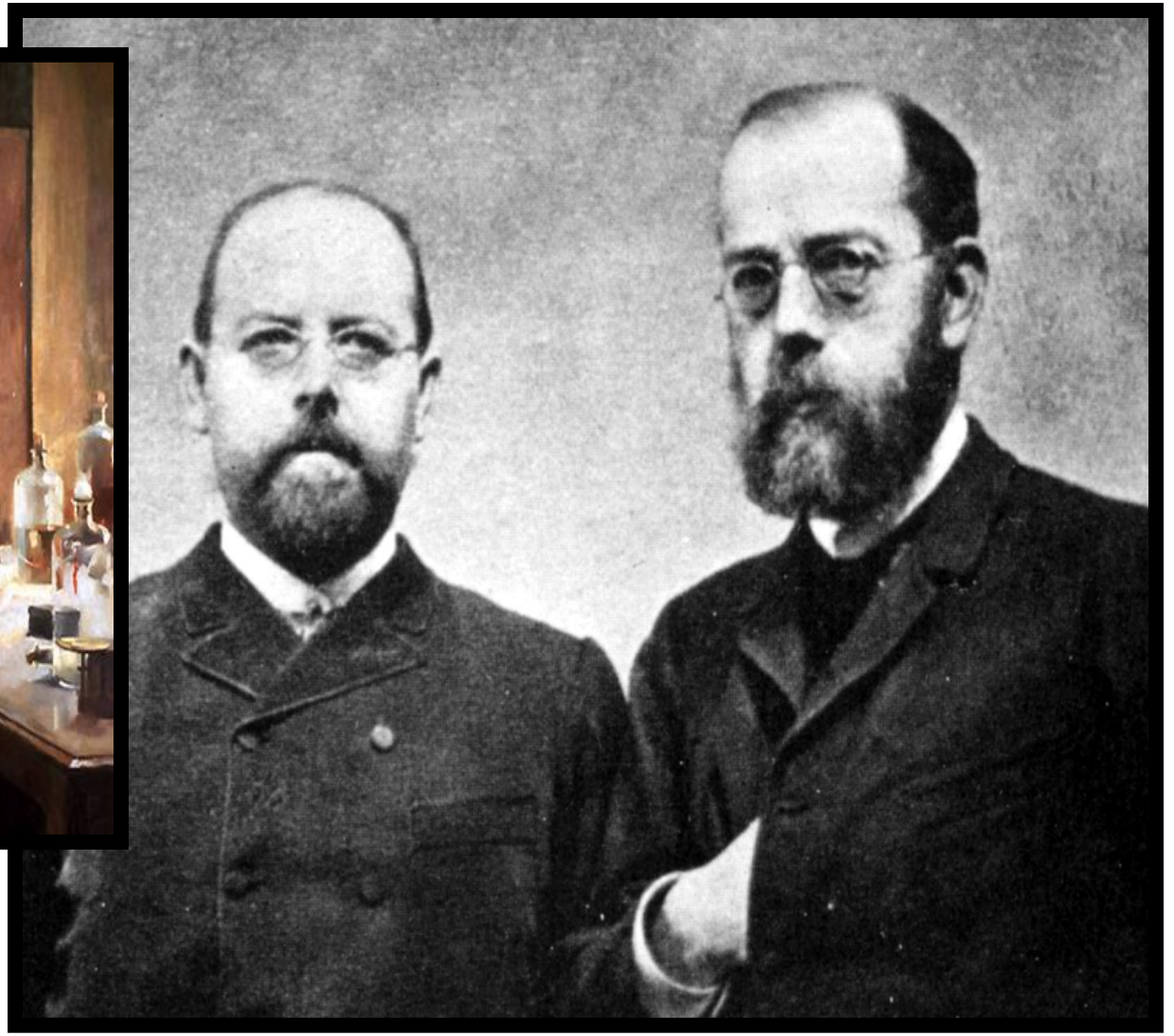


The Convergence Model. ***Microbial Threats to Health, Emergence, Detection and Response*** 2003

At the center is a box representing the convergence of factors leading to the emergence of an infectious disease.



Pasteur



Leitz 1890

Friedrich Loeffler (left) and P. Frosch, in 1898, identified the first virus of vertebrates, foot-and mouth disease virus, while working at the Robert Koch (right) Institute

The Nature of the Threat of New, Emerging & Re-emerging Infectious Diseases

- ***Microbial determinants***
  mutation, natural selection, evolution

- ***Determinants pertaining to the host***
  innate & acquired immunity

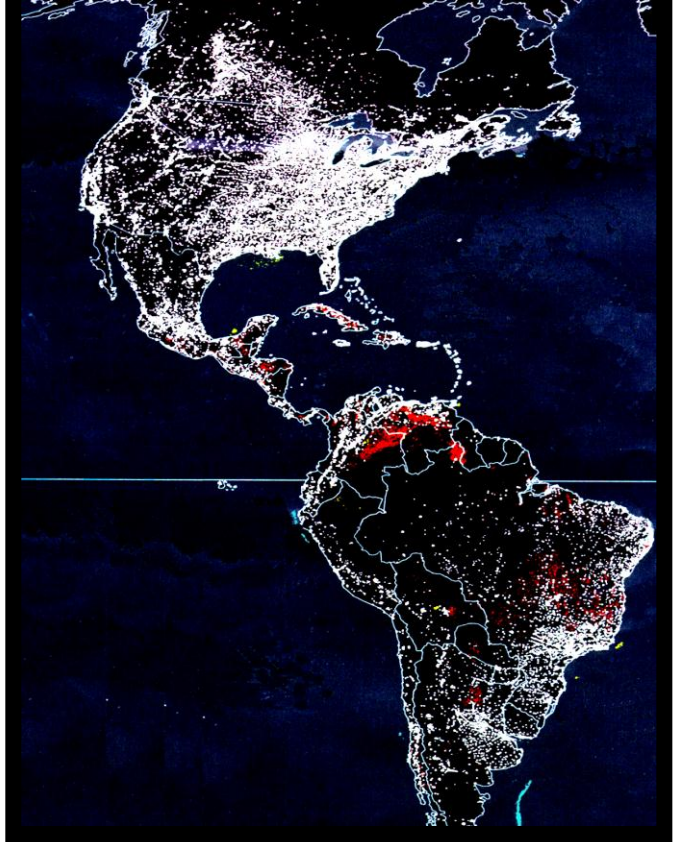
- ***Natural determinants***
  ecologic, environmental and climate, zoonotic influences

- ***Determinants pertaining to human activity (anthropogenic)***
  personal behavior, societal, commercial, and iatrogenic factors

- ***Accidental or malicious release***
  bioterrorism

There is one over-riding factor driving the emergence of diseases of humans & animals:

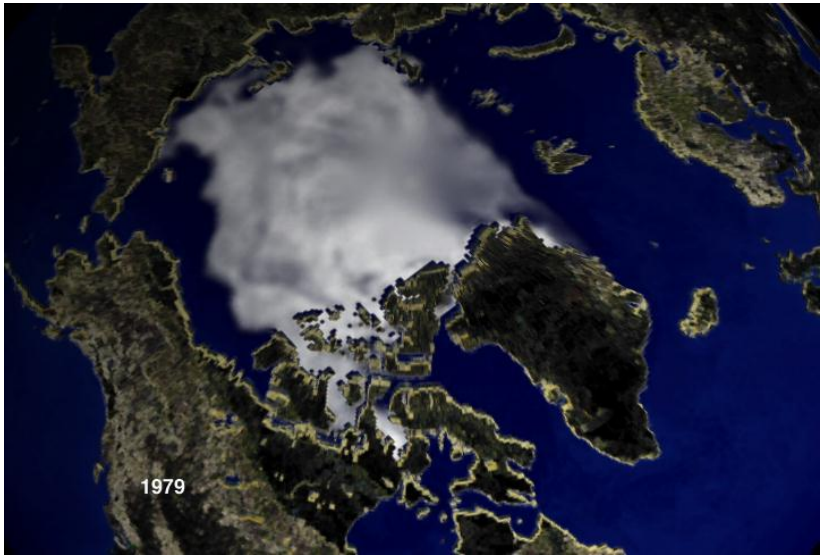
Human population growth and the incredible change occurring in all ecosystems brought about by human occupation of every corner of the planet

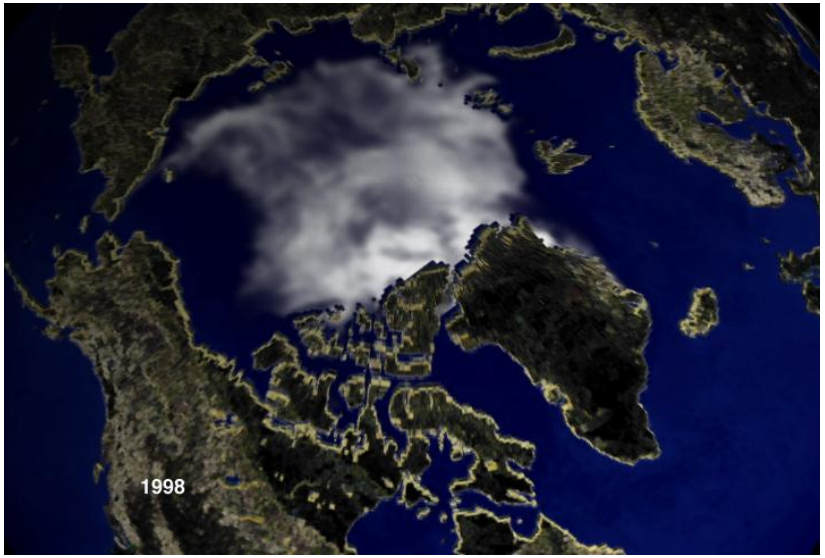


White = city lights
Yellow = natural gas burnoff
Red = fires
Blue = fishing lights

The World is an Increasingly Smaller Place in the 21st Century

http://www.youtube.com/watch?v=oR00_uLfGVE&feature=player_embedded#t=0s



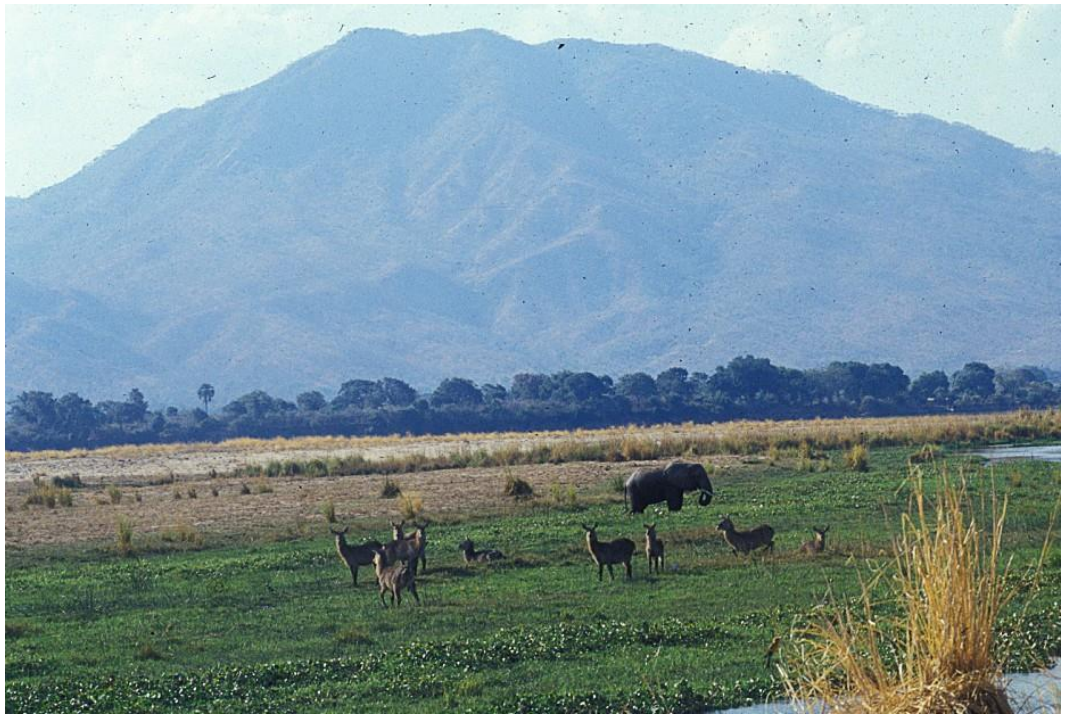


“Regardless of its origin, today there are unmistakable signs that the Anthropocene is turning ugly. So great are the changes scientists are detecting in our atmosphere that time’s gates appear once again to be opening. Will the Anthropocene become the shortest geological Period on record?”

Tim Flannery,

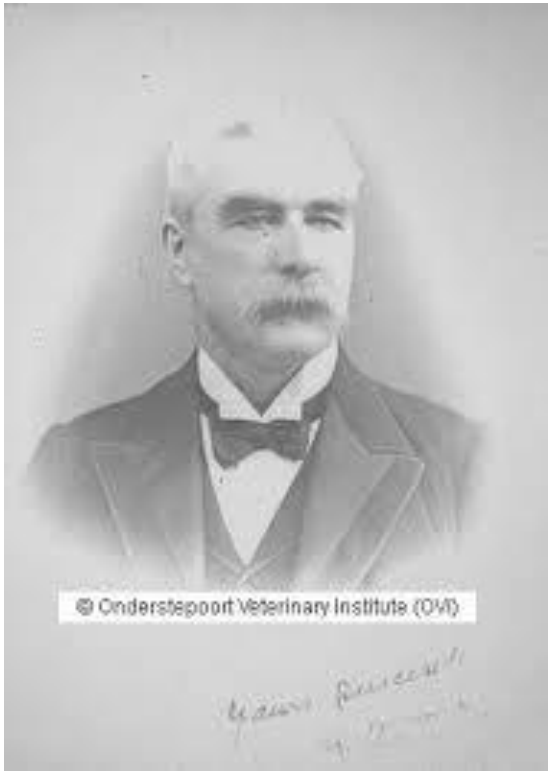
The Weather Makers, 2005

Bluetongue: An Historic Disease of Africa



Bluetongue: History

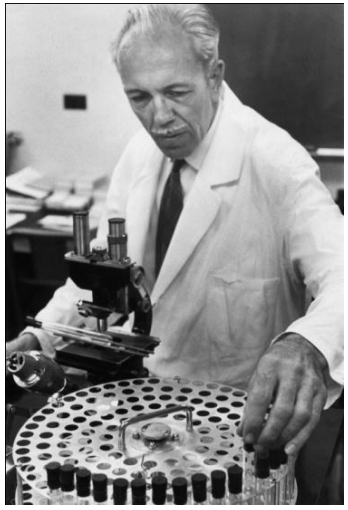
- **Insect-transmitted virus disease of sheep first described in South Africa (bloutong)**
  - **Hutcheon, 1881; Spreull, 1905**
  - **Cattle = asymptomatic reservoirs**
  - **Vaccine development circa 1900**
- **Later identified elsewhere**
  - **US in approx. 1950 – “soremuzzle”**
  - **Spread of diagnostic technology rather than the virus?**

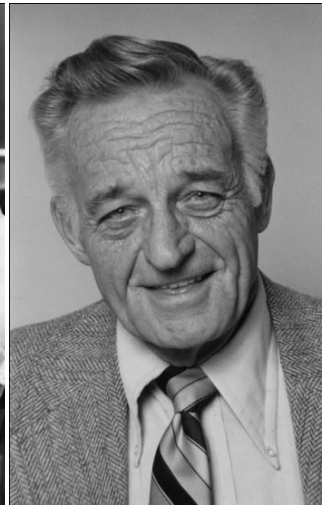


Bluetongue in California

- **First isolation of bluetongue virus in U.S.A. at UC Davis Veterinary School**

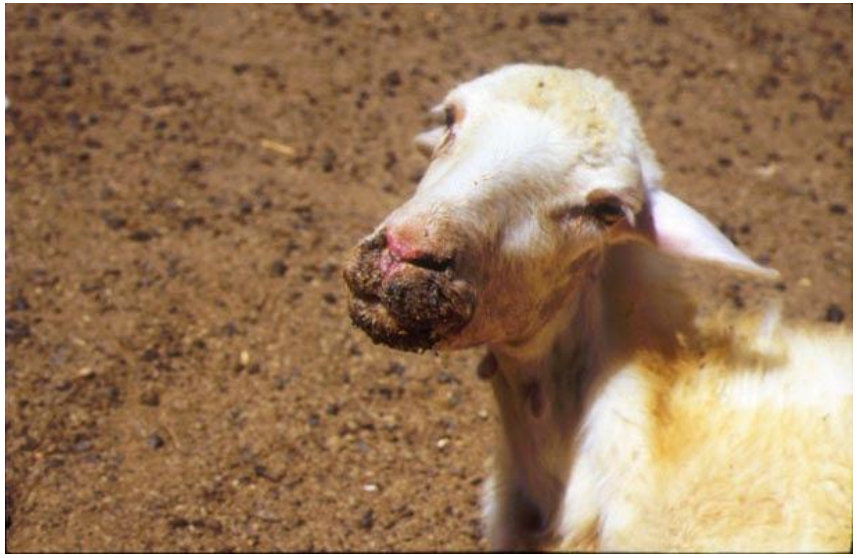
- **Vaccine development**
  - **Egg vaccine (McKercher *et al*., 1953) using techniques from Onderstepoort Veterinary Institute (Alexander *et al*.)**



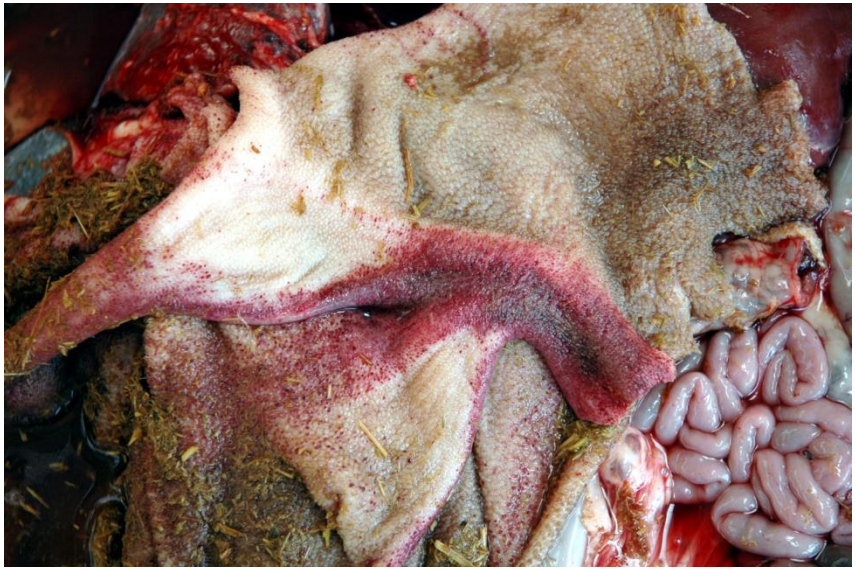
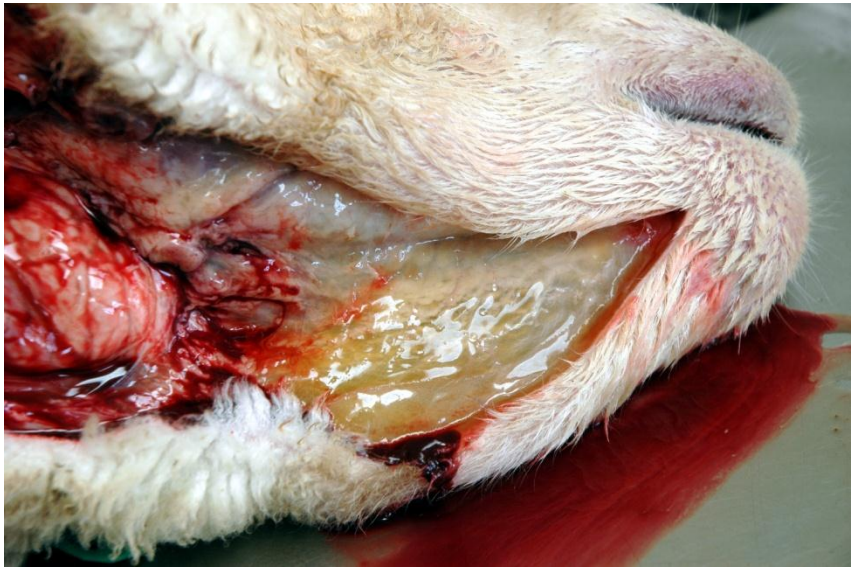


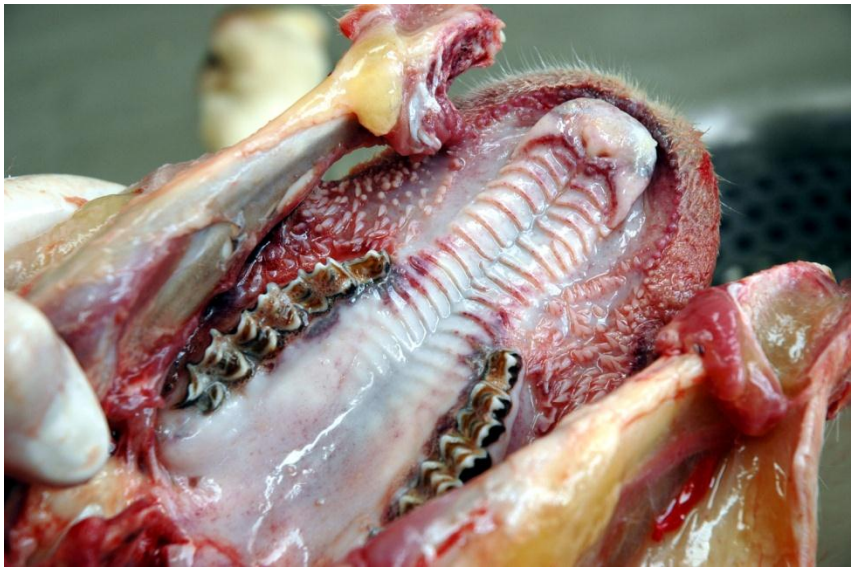
D. McKercher **B. McGowan**

Bluetongue: a Ruminant Viral Hemorrhagic Fever



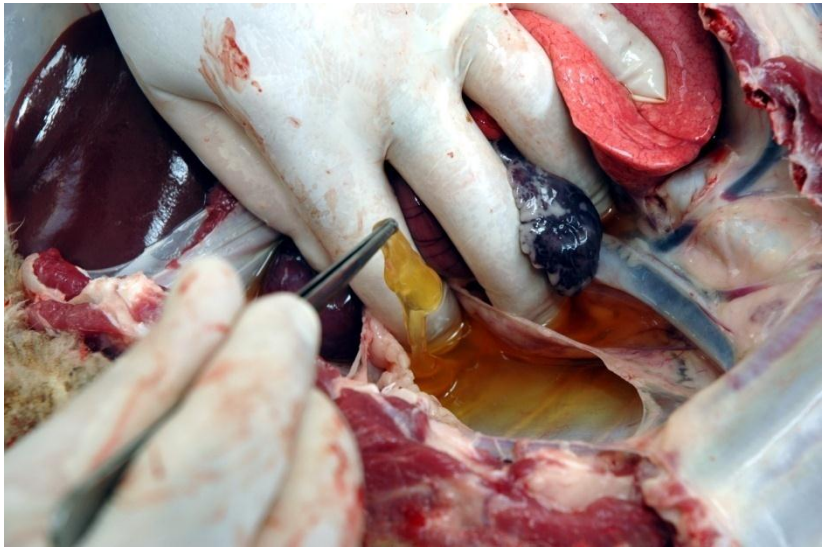
Ulcers, Hemorrhage and Edema

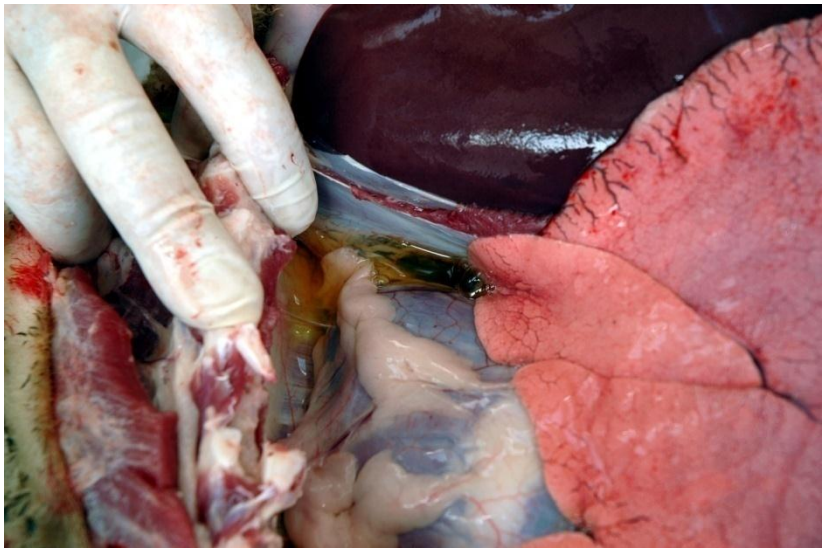





South African BTV serotype 4; *Vet Pathol*, 2008

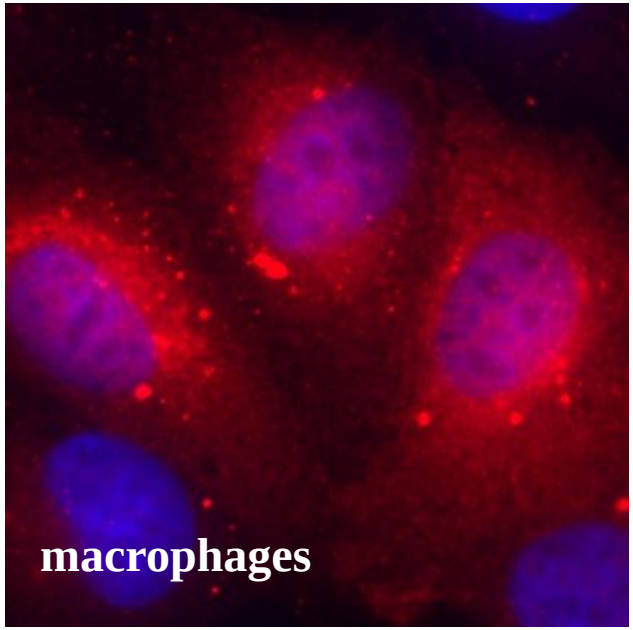
Pulmonary Edema: a Late (12 – 14 days after infection) and Fatal Manifestation

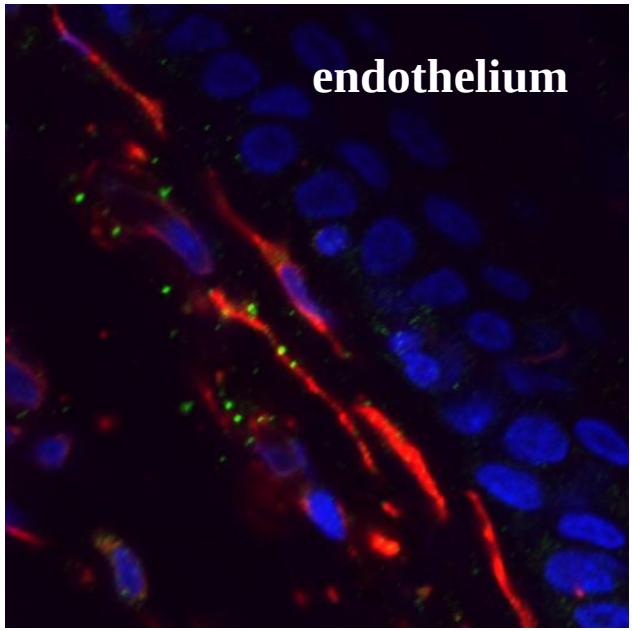




Bluetongue Pathogenesis: Virus Tropism = Dendritic Cells, Macrophages & Endothelium; Endothelial Injury Central to Disease Expression

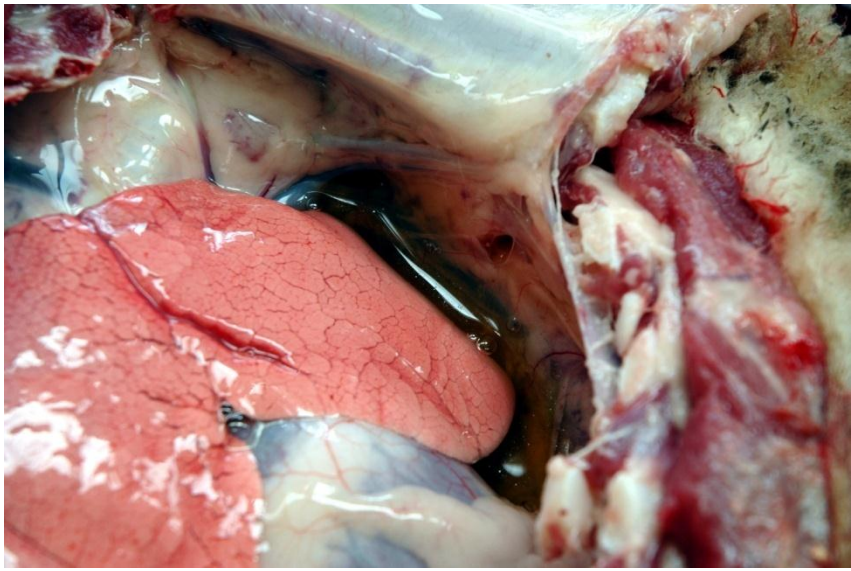
- BTV infection of macrophages & dendritic cells => TNF + other vasoactive mediators
  - Increase vascular permeability => capillary leakage => edema
- BTV => direct endothelial injury
  - Thrombosis and infarction





Consequences of BTV-induced Vascular Injury

- **Vascular permeability & capillary leakage**
  - **Subcutaneous, inter-muscular, pulmonary edema**
  - **Pleural/pericardial effusion**
- **Thrombosis & tissue infarction**
  - **Potentially DIC**
  - **Muscle necrosis**
    - **Cardiac and skeletal**
  - **Oral cavity ulcers, necrosis, hemorrhage (e.g. blue tongue)**



Human Viral Hemorrhagic Fevers

- **Reservoir hosts = wild or domestic mammals (except Dengue) that are typically unaffected**
- ***Arenaviridae***
  - **Lassa, South American (Junin, Machupo etc.) hemorrhagic fevers**
- ***Bunyaviridae***
  - **Rift Valley, Crimean Congo, Hantavirus, SFTS (severe fever with thrombocytopenia syndrome) hemorrhagic fevers**
- ***Filoviridae***
  - **Ebola, Marburg**
- ***Flaviviridae***
  - **Dengue & Omsk hemorrhagic fevers, Yellow fever etc.**

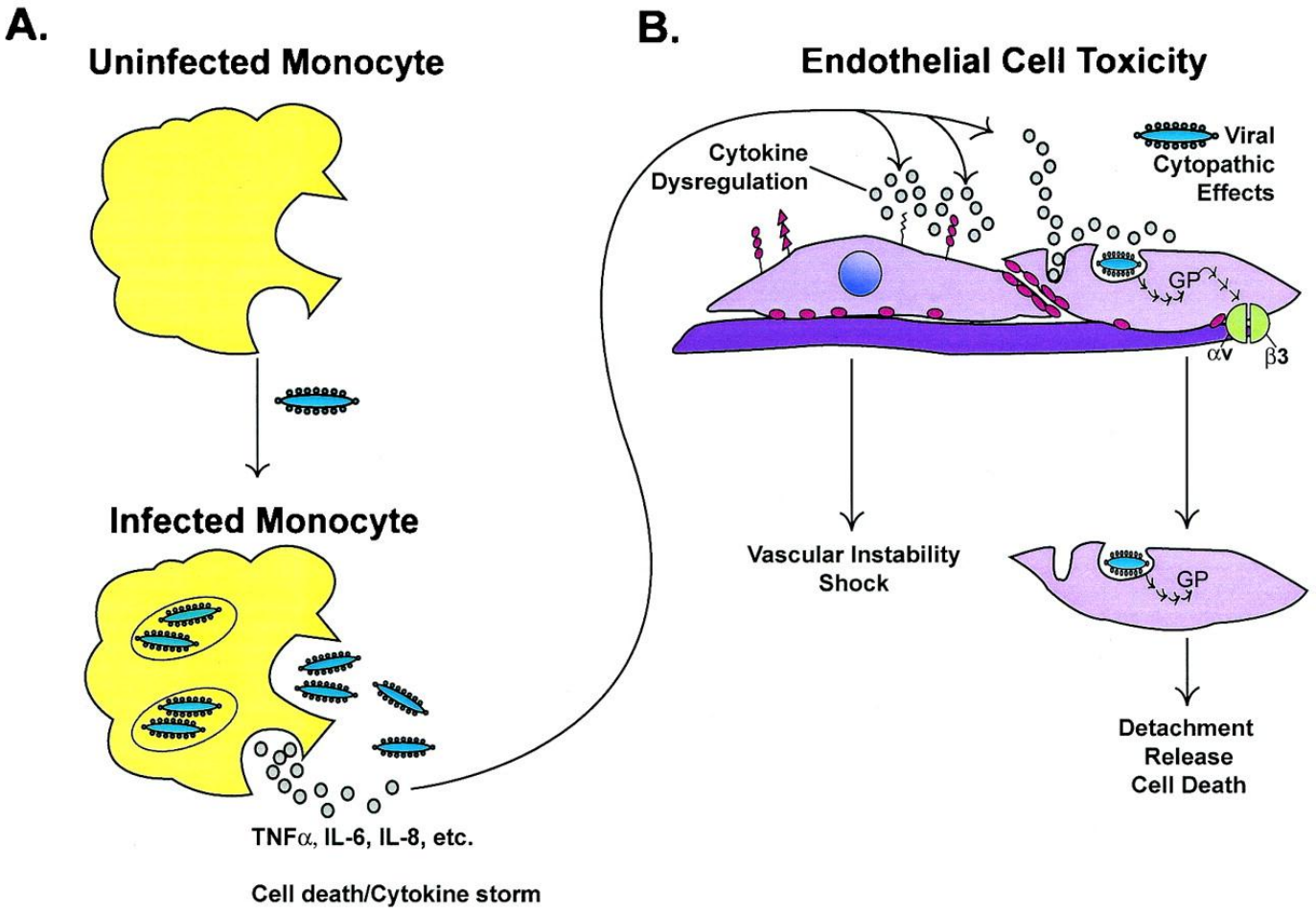
- **Many are certainly not new, re-emerging perhaps**
  - **Dengue, pandemic Africa/Asia/North America circa 1780**
    - **Philadelphia**
  - **Yellow fever, coastal Americas in 18th and 19th centuries**
    - **Substantial outbreak in Memphis, 1880**

Human Viral Hemorrhagic Fevers: Pathogenesis

- **Systemic infections with malaise, fever, ± hemorrhage**
- **Spectrum of disease - inapparent to mild (rash/arthralgia) to hemodynamic deterioration and shock**
  - **It is plasma volume loss that is catastrophic in these diseases!**
- **Pathogenesis poorly understood**
  - **Capillary leakage & hemorrhage**
  - **Thrombocytopenia**
  - **Role of endothelial infection versus cytokine mediators from virus infected macrophages/dendritic cells?**

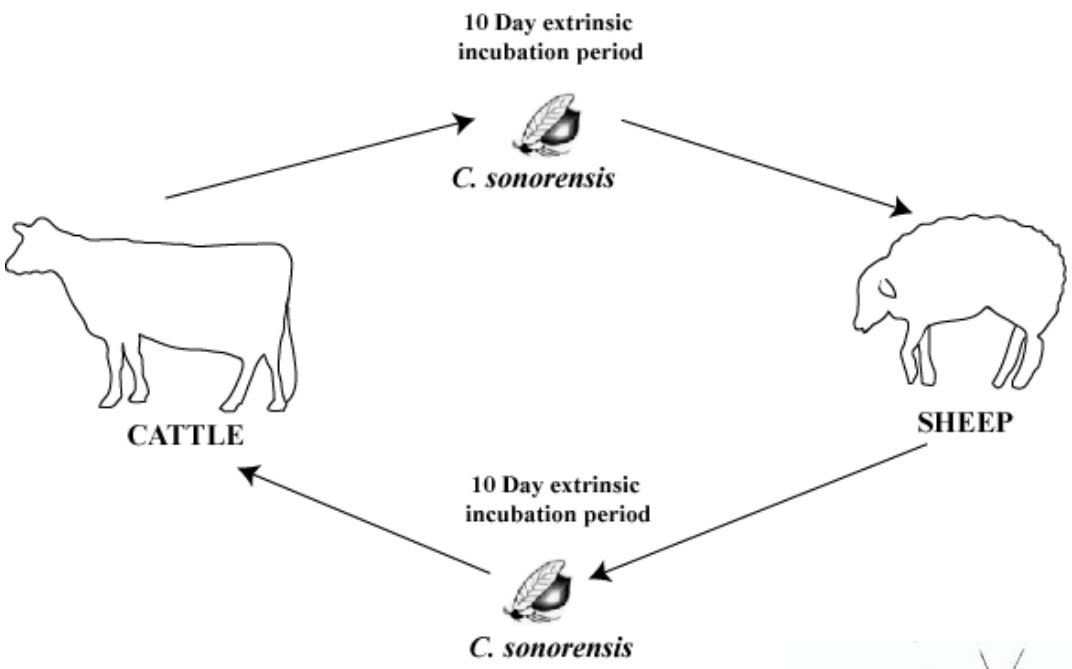
Meltzer, ***Infect Dis Clinics Nth Am 2012***

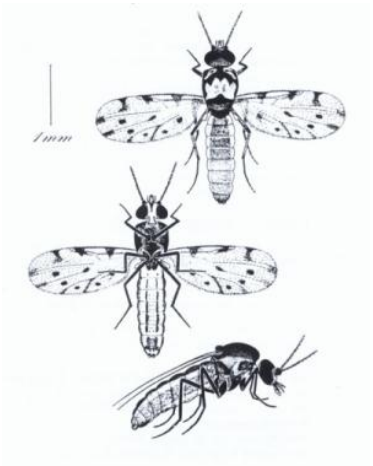
Generic Model of Viral Hemorrhagic Fevers, Bluetongue Included?



Ebola - Sullivan et. al., *J Virol*, 2003; Bluetongue: Maclachlan et al, *J Comp Pathol*, 2009

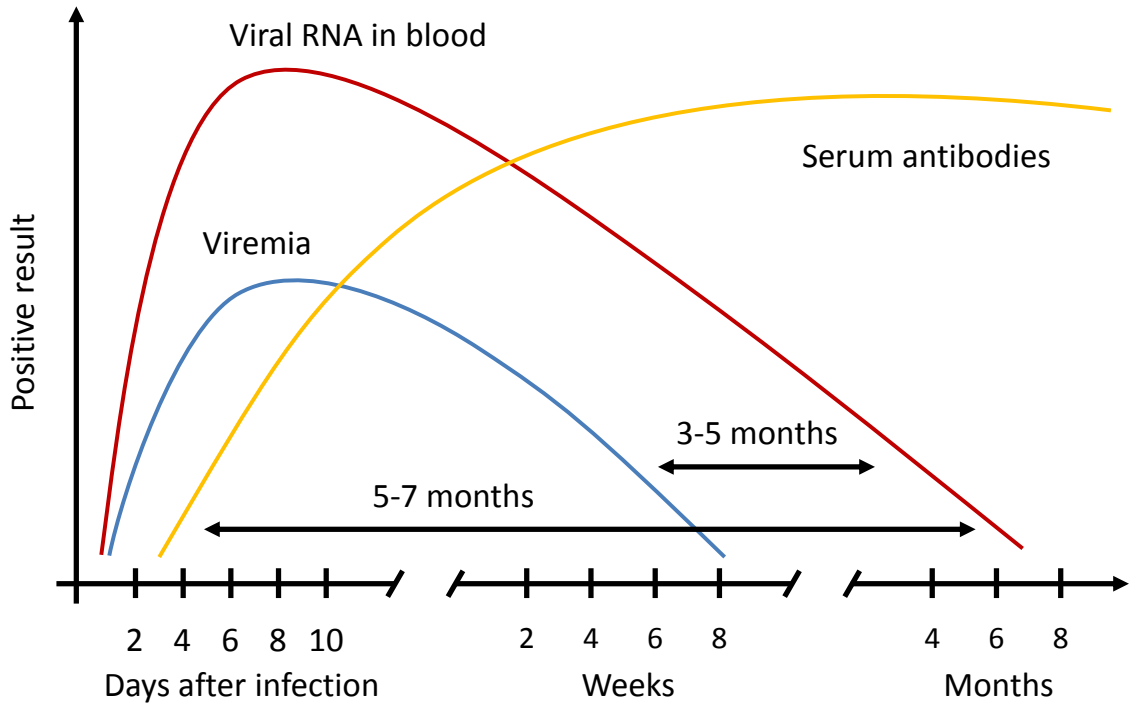
The Cycle of Bluetongue Virus: Usually a <u>Non-contagious</u> Infection

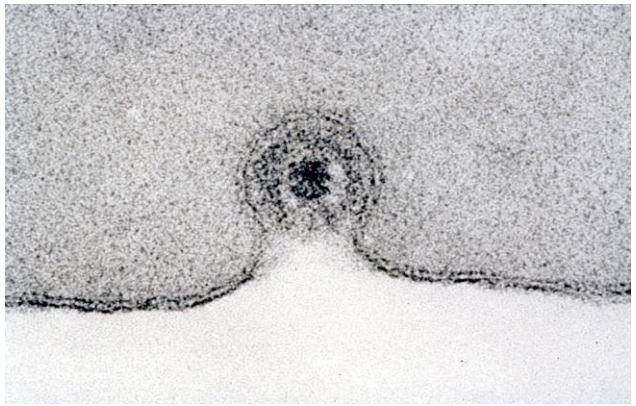


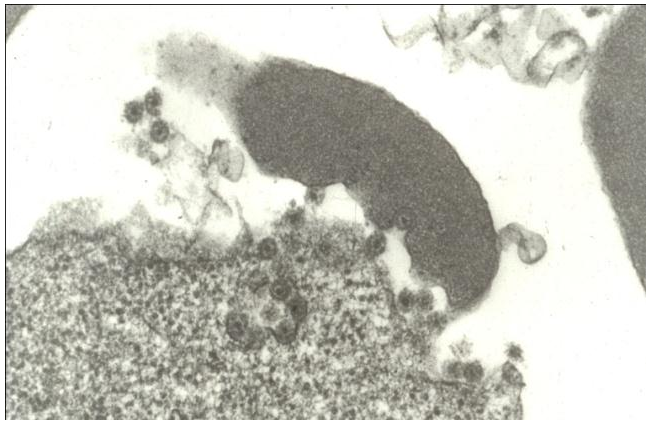


- ***Culicoides* sp. = biological vectors**
  - **Few of > 1000 *Culicoides sp.* worldwide are proven vectors of BTV – <u>changing with climate alteration?</u>**
- **All ruminants, wild and domestic, plus:**
  - **Dogs – contaminated vaccines**
  - **African & Eurasian carnivores**
  - **South American camelids**

BTV Infection can be Prolonged in Ruminants; Association of Virus with Erythrocytes







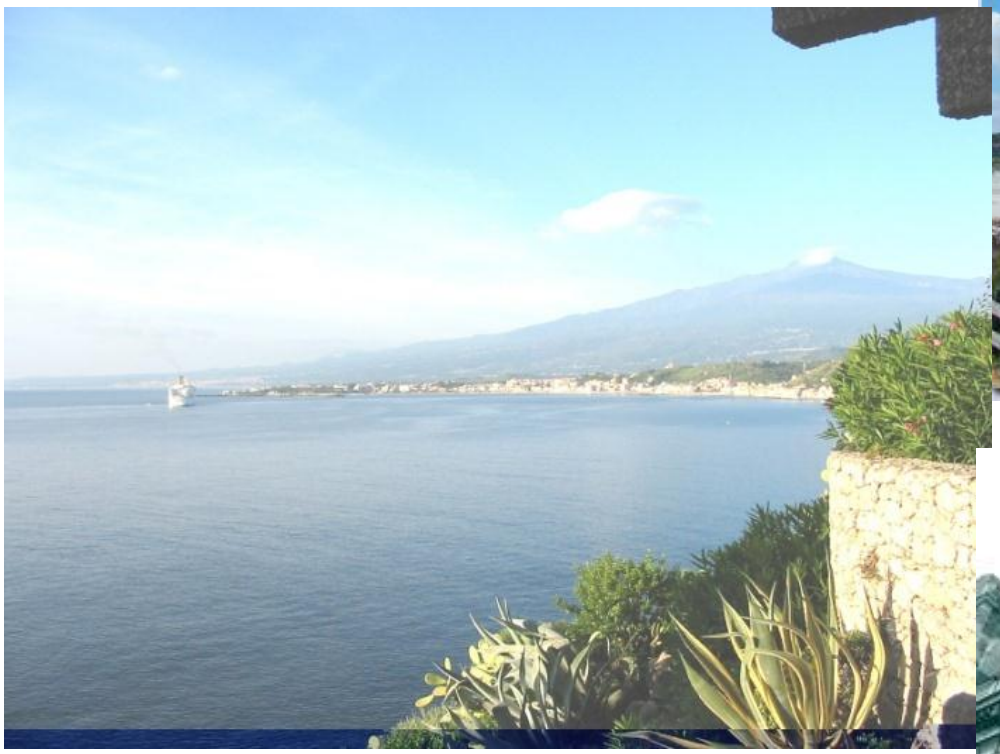
Courtesy of M. Eschbaumer and B. Hoffmann

Persistent BTV Infection of Cattle: A FAILED SCENARIO to Explain the Dissemination and "Over-wintering" of BTV

Dogma of the 1960s; BT = emerging disease spread by animal movement and trade. No thought of spreading diagnostic technology from South Africa

Now discredited theory that congenital BTV infection => persistently infected, immunologically tolerant cattle that served as virus reservoirs

OIE Symposia on Bluetongue and Related Orbiviruses

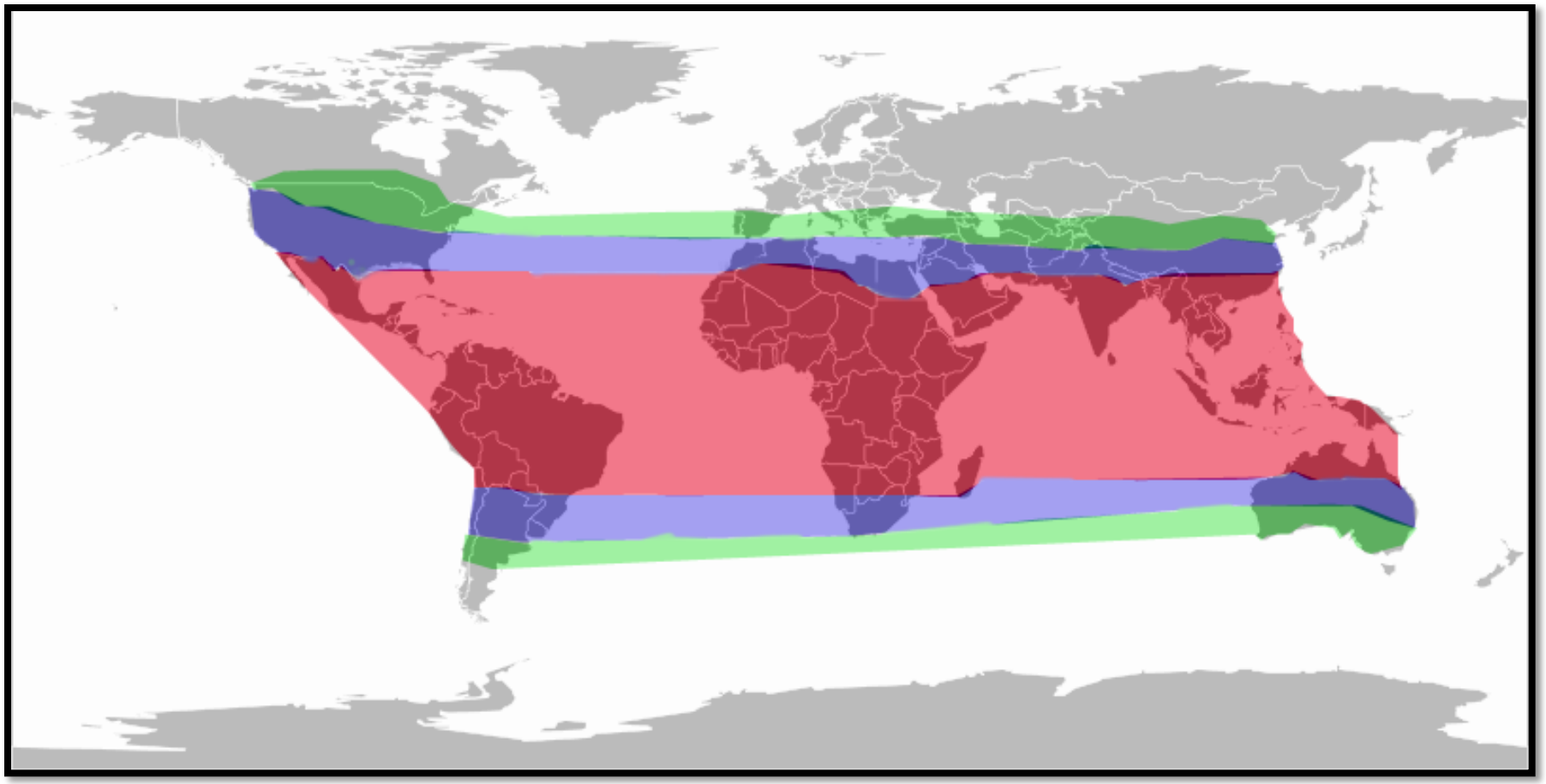


Taormina, Sicily, 2003

Asilomar, California, 1984

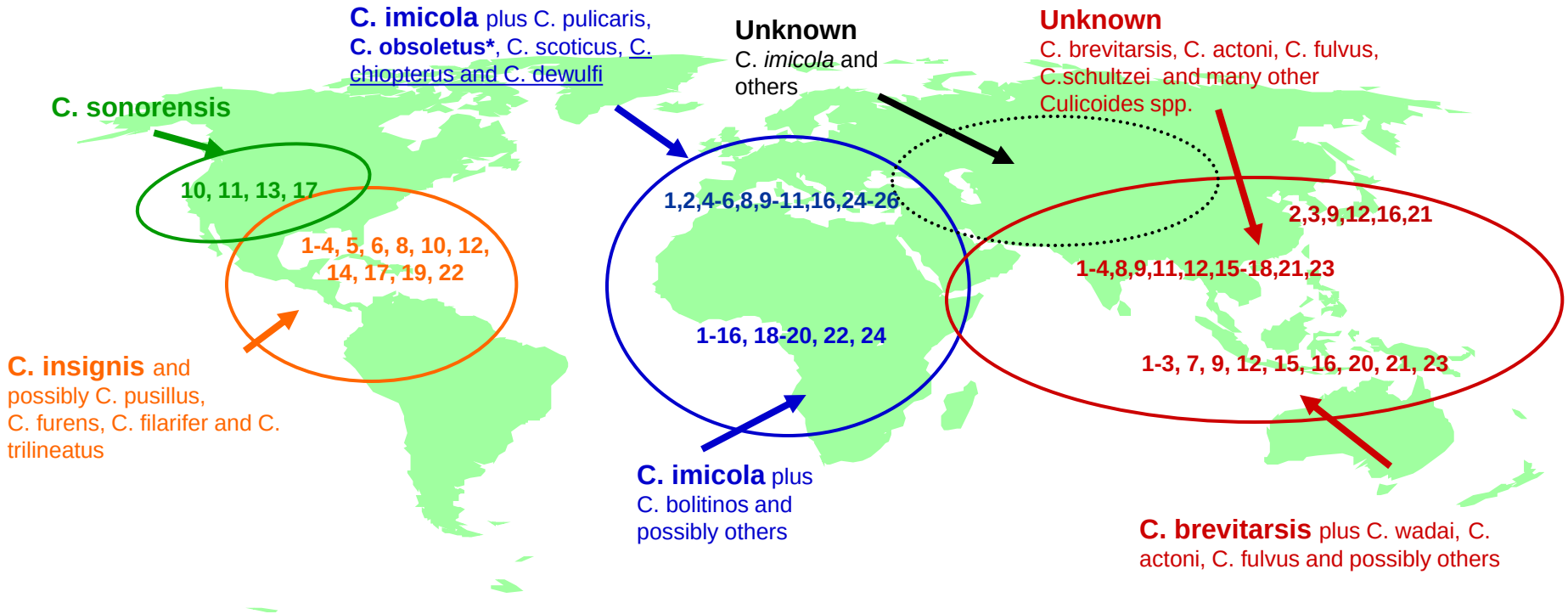
OIE, Paris, 1991

Global Distribution circa 1990



Gibbs and Greiner, 1994

BLUETONGUE GLOBAL ECOSYSTEMS



Different species of *Culicoides* vector disseminate different BTV serotypes in distinct global ecosystems (episystems)

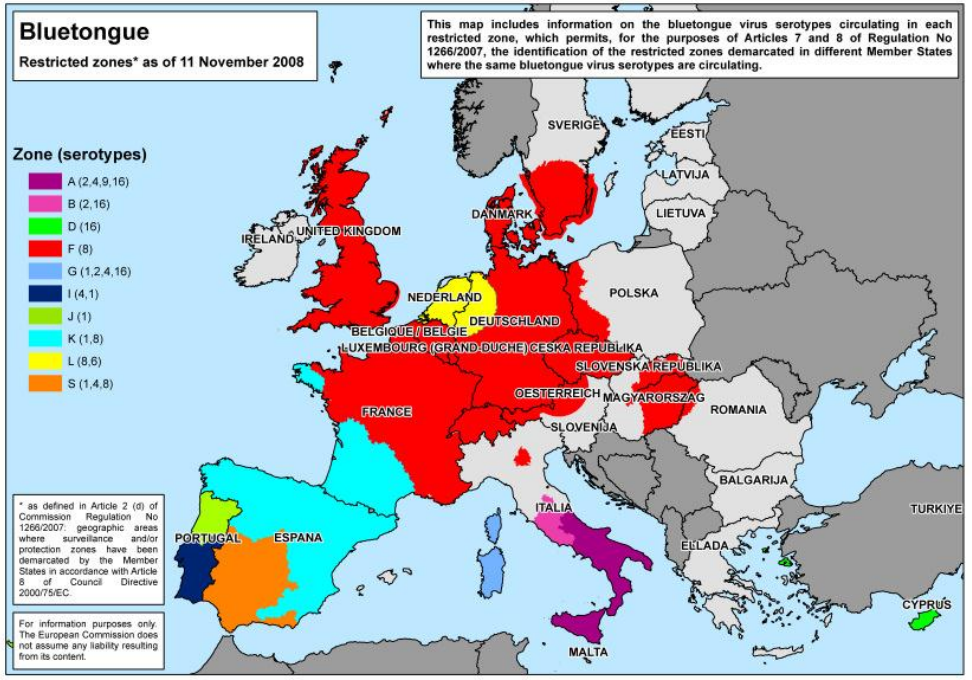
•Bold indicates known or presumed principal vector

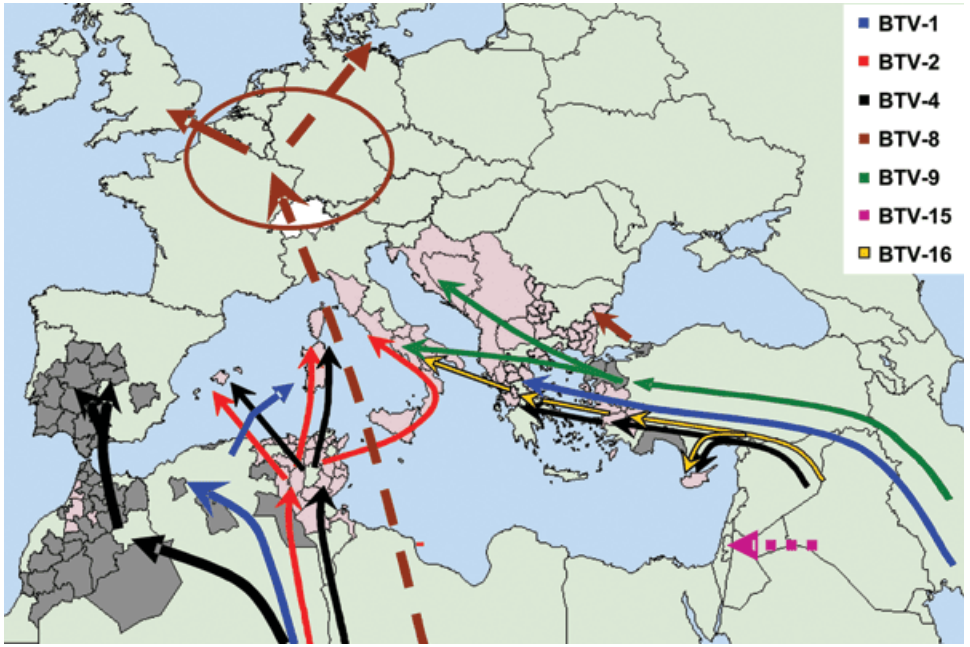
Global Emergence of Orbiviruses

- **Bluetongue**
  - **Europe (8 serotypes) plus Toggenberg (serotype 25), Middle East (2 new serotypes in Israel) plus serotype 26 (Kuwait), Australia (2 new serotypes), U.S. (10 new serotypes in the southeast)**
- **Epizootic hemorrhagic disease**
  - **North Africa and Middle East; disease in cattle**
  - **US; serotype 6 in the mid-West as far north as Michigan – disease in deer and cattle**
- **Equine encephalosis (Theiler's "Ephemeral Fever")**
  - **Israel**
- **Peruvian horse sickness and Yunnan orbivirus**
  - **Disease in horses in South America and Australia (Elsey virus)**
- **Seadorna viruses among humans in China (Bannavirus)**

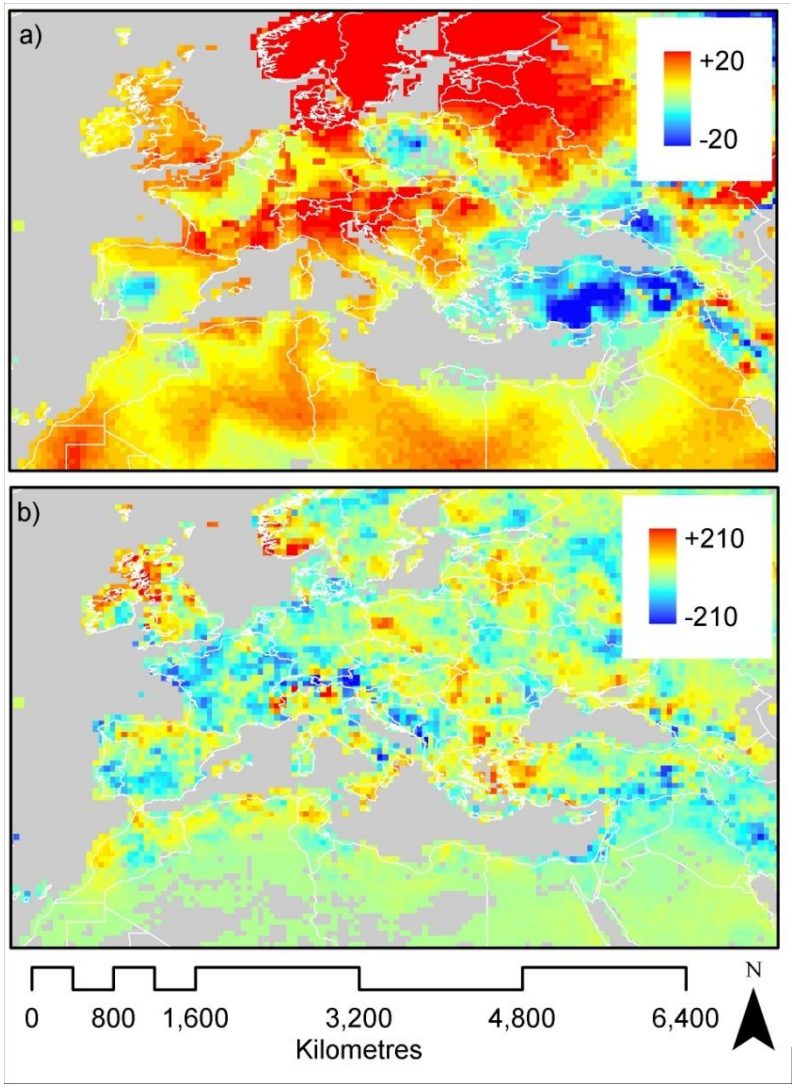
Bluetongue in Europe 2008

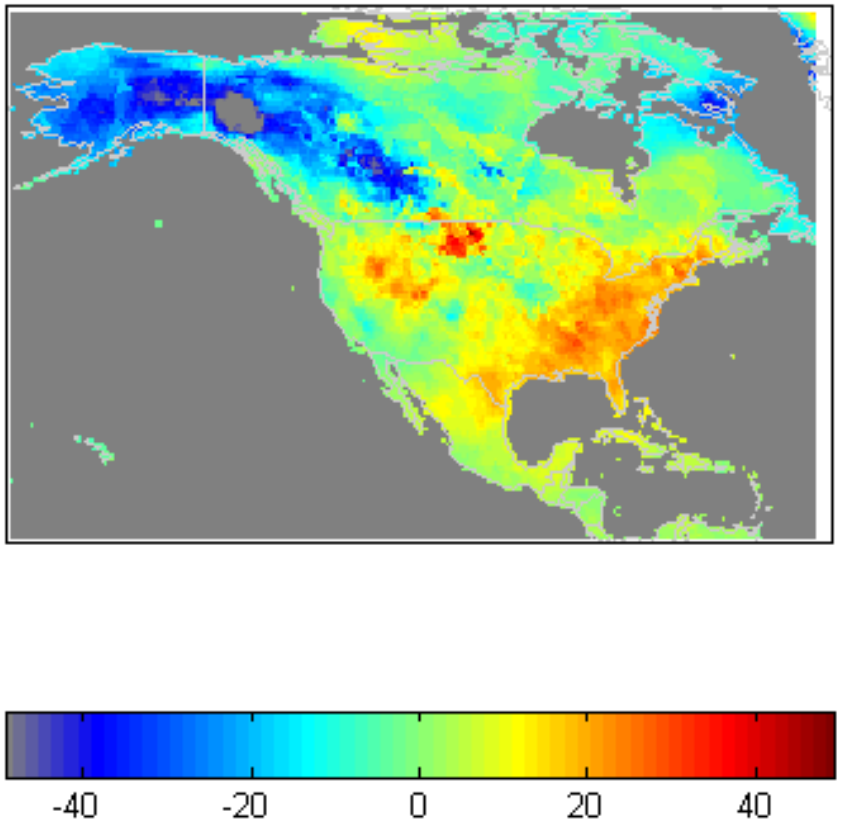
- Originally 5 serotypes in Mediterranean Basin since 1998; 3 in northern Europe since 2006
  - Serotype 8 especially virulent to sheep, cattle, and non-African wild ungulates
- Now endemic in some countries, not others
- <u>Why now?</u>





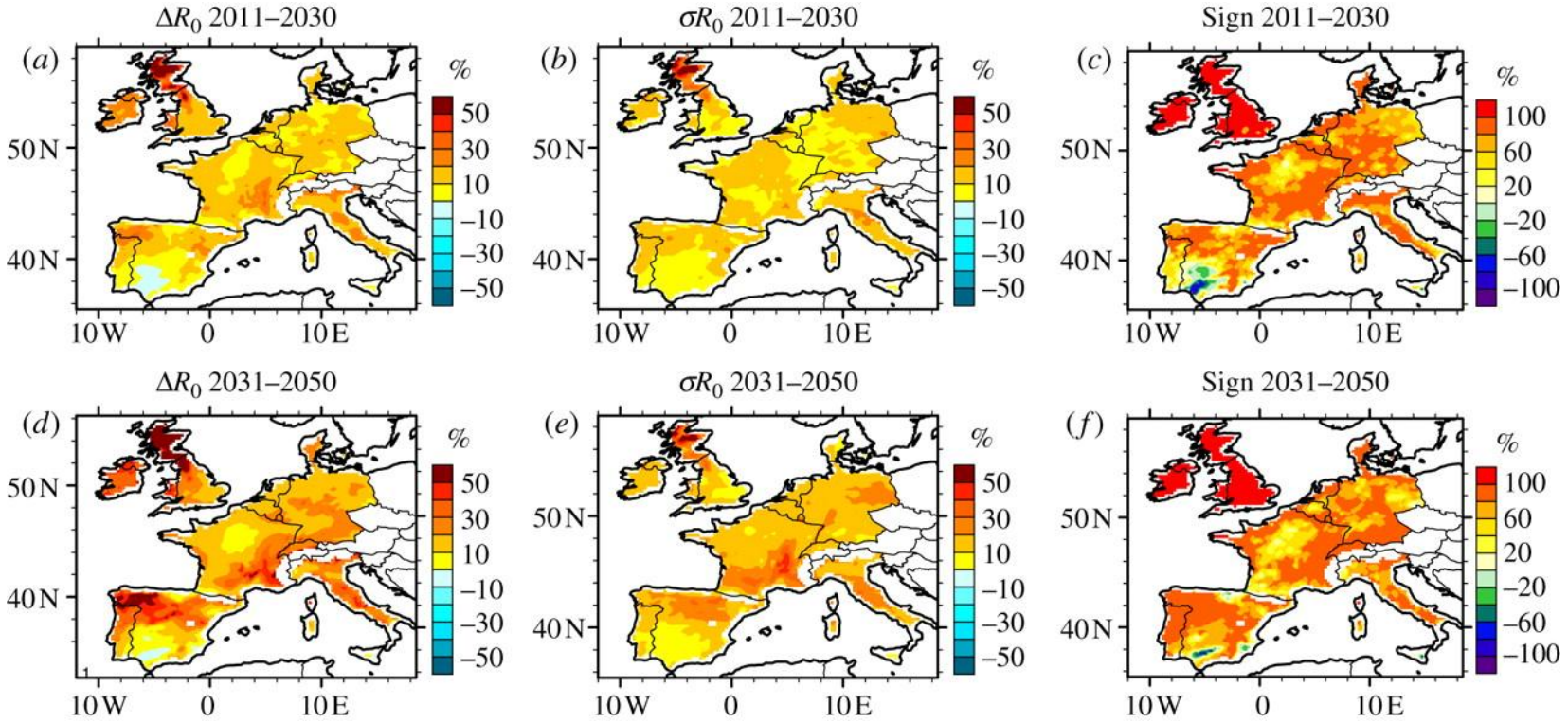
Climate Change: Is Bluetongue a Portent of Things to Come or a One-off Event?





Purse et al., *Nature Rev Microbiol*, 2005; *Rev Sci Tech*, 2008

Simulated R0 changes, spread and sign consistency.



Conclusion = by 2050, in northern Europe there could be a 17% increase in occurrence of BTV, compared with 7% in southern regions, where it is already much warmer.

Guis H et al. J. R. Soc. Interface doi:10.1098/rsif.2011.0255

JOURNAL OF THE ROYAL SOCIETY Interface

The Larger Message of Bluetongue?

- **Is bluetongue the "point of the spear" in global emergence of arboviruses driven by climate change?**
  - **Multipe regions, multiple serotypes – Europe, North America, Australia, Middle East and Asia**
  - **In Europe, existing *Culicoides sp.* now transmit BTV = WHY? Climate change?**
    - **And now Schmallenberg virus too, why?**
- **The future?**
  - **African horse sickness and other orbiviral diseases**

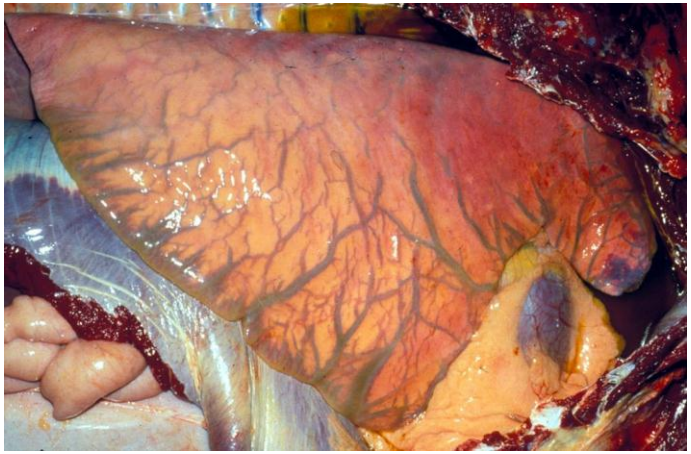
African Horse Sickness

- **Perhaps the most internationally feared contagious disease of equids**

- **Epidemiology similar to BTV**
  - **Sub-Saharan Africa, incursions into Mediterranean Basin, Middle East and Asia**
  - ***C. imicola, C. bolitinos* but others competent in lab; impact of climate change?**

- **Viral Hemorrhagic Fever like BT**
  - **Profound edema = capillary leakage**
  - **Virus infection of macrophages, endothelium (incl. pulmonary intravascular macrophages); Clift and Penrith, *Vet Pathol* 47: 690-697, 2010**

African Horse Sickness





Courtesy A. Guthrie and W. Laegreid

Protective Immunization of Horses with a Recombinant Canarypox Virus Vectored Vaccine Co-expressing Genes Encoding the Outer Capsid Proteins of African Horse Sickness Virus

Guthrie et al., *Vaccine,* 2009

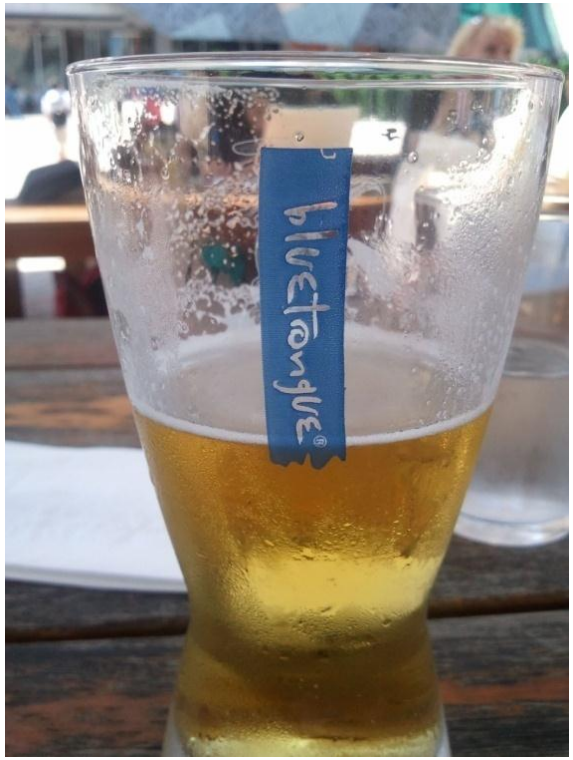
- Protection of horses
- DIVA capability (VP7 ELISA)
- Familiar commercial vector

Sad history of all our failures (bluetongue too) = Maclachlan & Guthrie, *Vaccine*, 2007

Where to Next?

- **The glass > half full; Theiler would relish the challenge!**

- **Identify environmental-host-virus factors => expression & spread of emerging livestock diseases – then design strategies to prevent or mitigate them**



bluetongue BREWERY

THANK YOU!

- **Dean Swan, Prof Coetzer, and the Veterinary Faculty**
- **Prof Alan Guthrie, colleagues & staff at Equine Research Center**
- **Veterinary Tropical Diseases**
  - **Estelle Venter, Jannie Crafford, Melvyn Quan, etc.**