Be-FAST and Be-CoDiS: mathematical models to predict the spread of human and livestocks diseases with real data. Application to the 2014 Ebola Virus Disease epidemic and livestock diseases

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Partnership

- CSF in Segovia (Spain):

GOBIERNO DE ESPAÑA
MINISTERIO DE MEDIO AMBIENTE Y MEDIO RURAL Y MARINO
Junta de Castilla y León
Diputación de Segovia

- CSF in Bulgaria:

BULGARIAN FOOD SAFETY AGENCY
SAFETY EVERY DAY
BFSA

- FMD in Peru:

GOBIERNO DE ESPAÑA
MINISTERIO DE AGRICULTURA, ALIMENTACIÓN Y MEDIO AMBIENTE
ENESA
Entidad Estatal de Seguros Agrarios

CONTROL PROGRESIVO DE LA FIEBRE AFTOSA
Cooperazione Italiana allo Sviluppo
Ministero degli Affari Esteri
FAO FIAT PANIS
MINISTERIO DE ASUNTOS EXTERIORES Y DE COOPERACIÓN
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Outline

- A short introduction to epidemiology

  -Basic concepts
  -A classical model: S.E.I.R. model

- Be-FAST model

  -Hybrid S.I. / Individual Based model
  -Applications to CSF and FMD

- Be-CoDiS model

  -S.E.I.H.R. model / migratory flow
  -Application to the 2014 Ebola Virus Disease epidemic

- Conclusions and perspectives

Part I: A short introduction to epidemiology

Basic definition

The epidemiology is the study of the distribution and determinants (i.e., causes of infection) of prevalence (i.e., affected population) of the diseases in humans or animals (veterinarian).

The main objectives of this discipline are:

- Describe the distribution (i.e., where? when? How many?) of a disease. In particular, to know whether the outbreak will be endemic (i.e., does not disappear) or not.
- Identify the risk factors or determinants in order to explain the non-uniformity.
- Preventive role: Plan, implement and evaluate detection, control and prevention programs.

Here, we focus on the epidemiological modelling: Mathematical models that simulate the spatial and temporal evolution of a disease outbreak.

Historical context

Some important historical results:

- 1760 - Daniel Bernouilli: a first mathematical model to study the efficiency of the smallpox virus variolation in healthy people in Turkey.
- 1906 - William Heaton Hamer: a discrete time model to explain the recurrence of measles (Sarampion) epidemics in England: introduce a dependence between the disease incidence and the product of the densities of the susceptible (non-contaminated) and infective people.
- 1911 - Ronald Ross: PDE model to study the link between malaria and mosquitoes: help to eradicate this disease in Europe.
- 1926 - Mc Kendrick and Kermack: Prove that density of susceptible people must exceed a critical value in order for an epidemic outbreak to occur.

Current challenges

Currently the number of models is widely increasing in order to study the actual important diseases:

- New diseases: Ebola, S.R.A.S., Influenza, HIV...
- Re-emergent diseases: Malaria, Syphilis, Tuberculosis...

Those models are based on various mathematical tools: Dynamical systems, Montecarlo algorithms, Networks, Markov processes,...

They are complex and can now take into account various disease properties such as: passive immunity, gradual loss of immunity, stages of infection, disease vectors, age structure, mixing groups, spatial spread, vaccination, quarantine...

A classical model: S.E.I.R.

We briefly present one of the classical models in epidemiology: the 'S.E.I.R.' model.

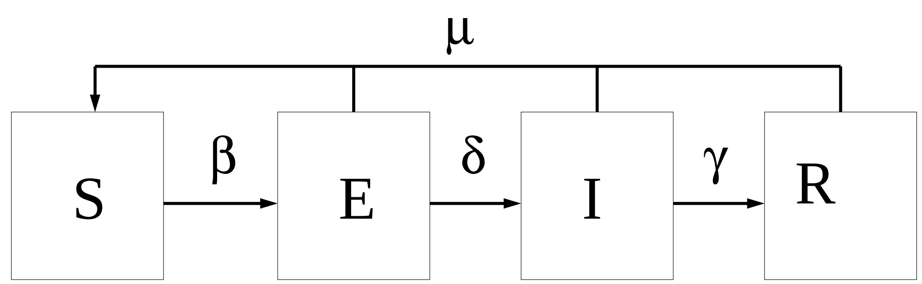
It is a compartment model that simulates the temporal evolution of the population proportion in each compartment taking into account the flow between them.

Example: considering a virus type disease, we assume that each individual in the population is in one of the following compartments:

- S - Susceptible: free of disease.
- E - Infected (or Exposed): in latent phase, can't infect other people.
- I - Infectious: can infected other people.
- R - Recovered: have an immunity against the disease: can't be infected.

A classical model: S.E.I.R.

The diagram of the considered flow can be:



Those flows follow the equations:

$$\begin{cases} \frac{\mathrm{d}S(t)}{\mathrm{d}t} = -\beta\frac{I(t)}{N}S(t) + \mu(E(t)+I(t)+R(t)), \\ \frac{\mathrm{d}E(t)}{\mathrm{d}t} = \beta\frac{I(t)}{N}S(t) - (\delta+\mu)E(t), \\ \frac{\mathrm{d}I(t)}{\mathrm{d}t} = \delta E(t) - (\gamma+\mu)I(t), \\ \frac{\mathrm{d}R(t)}{\mathrm{d}t} = \gamma I(t) - \mu R(t), \end{cases}$$

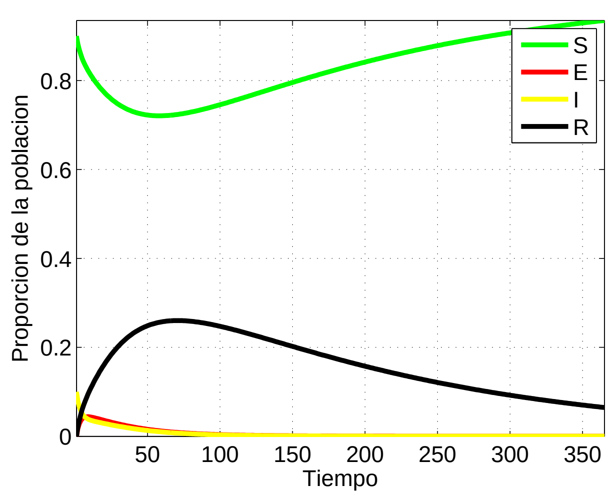
where β is the disease effective contact rate (time^{-1}); δ and γ are transition rates (time^{-1}); μ is the mortality/natality rate (time^{-1}).

A classical model: S.E.I.R.

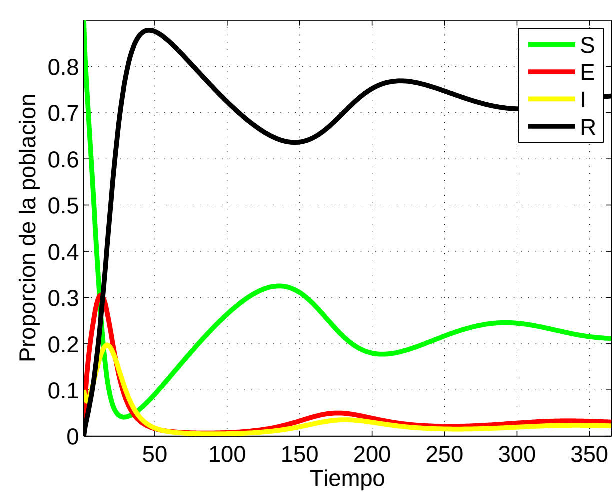
We can compute the basic reproduction number R_0 that indicates whether the outbreak is endemic or not.

In our particular case $R_0 = \frac{\beta\delta}{(\delta+\mu)(\gamma+\mu)}$ and we can proof (by linearization) that there is a globally asymptotically stable disease-free equilibrium if $R_0 \leq 1$ and there is a locally asymptotically stable endemic equilibrium when $R_0 > 1$ (if we start in a defined admissible space).

$R_0 \leq 1$



$R_0 > 1$



A classical model: S.E.I.R.

Advantages of the S.E.I.R. models:

- Computationally low.
- Allow to have a quick idea of the outbreak behavior.

Main drawbacks:

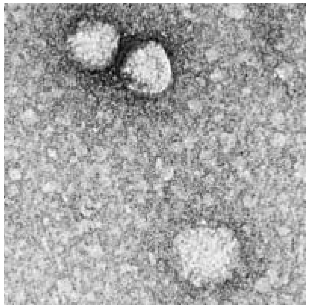
- Valid for spatial environments with a homogeneous population density distribution (for instance, inside a farm).
- Do not take into account efficiently the spatial diffusion of the outbreak (it can be simulated by using a cluster structure).

Our idea: take the advantages of this technique (simulate the spread within a farm/country) and combine it with a more complex model (simulate the spread between farms/countries).

Part II: Be-FAST model

Considered diseases: Classical Swine Fever

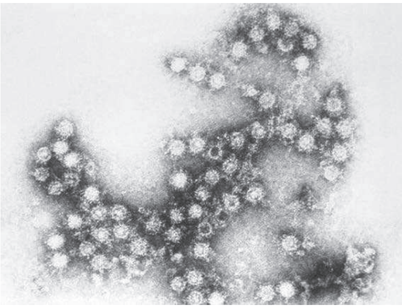
- Classical Swine Fever (CSF) is a non-zoonotic highly contagious viral disease of domestic and wild pigs caused by a *Flaviviridae Pestivirus*.



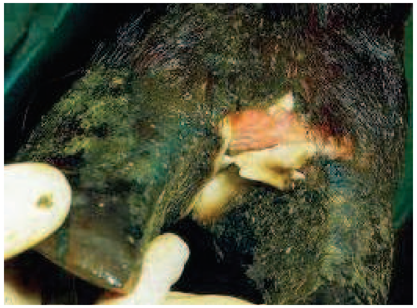
- Infected animals present various symptoms (fever, lesions, hemorrhages...) provoking a disease mortality of ≈ 30% up to 100% (depending on the strain).

Considered diseases: Foot-and-Mouth Disease

- Foot-and-Mouth Disease (FMD) is a highly contagious viral disease of cloven-hoofed animals (bovine, sheep, swine, camelid, etc.) caused by a *Picornaviridae virus* which can rarely contaminate humans.

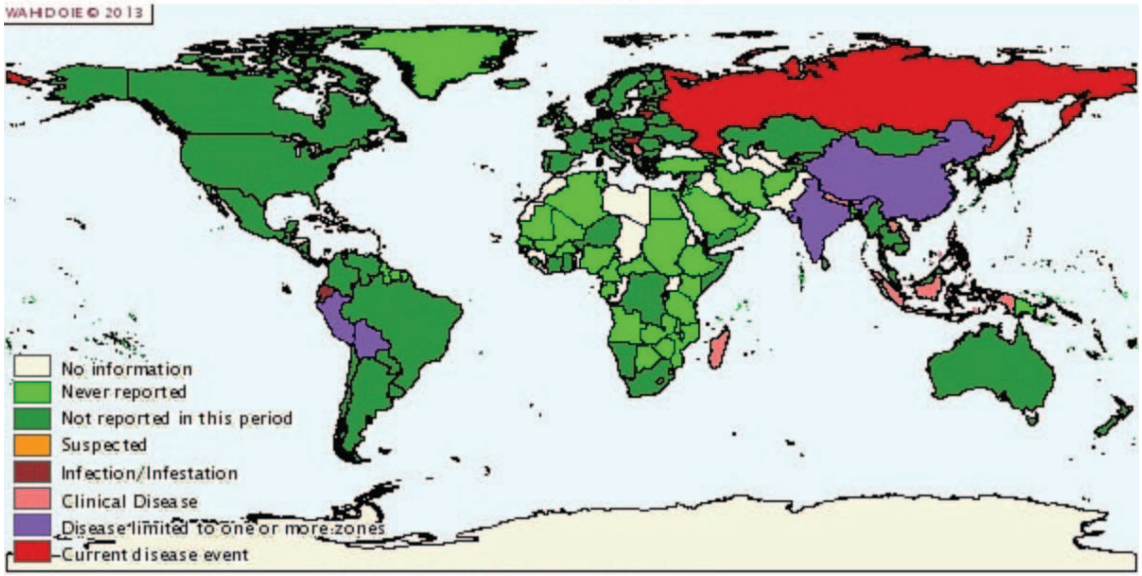


- Infected animals present various symptoms (blisters, severe weight loss, myocarditis ...) provoking a disease mortality of ≈ 20%-50% for adults and 25%-90% for juveniles

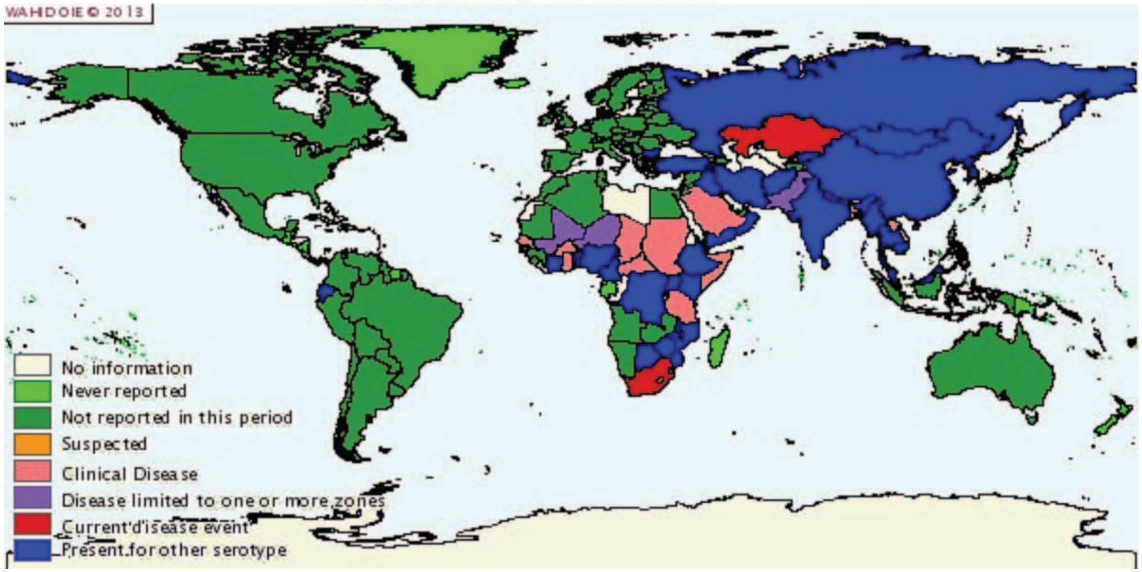


Considered diseases: Global Situation

CSF (2011) - Source OIE



FMD (2011) - Source OIE



Objective of the work

Develop an epidemiological model for livestock diseases, called Be-FAST (Between Farm Animal Spread Transmission), which can be adapted to each specific case (disease, region, etc.) in order to:

- Analyze the patterns of the spread between farms.
- Characterize the risk areas of disease introduction/spread.
- Estimate the economical losses generated by the epidemics (useful for insurance companies and authorities).
- Evaluate the efficiency of control measures (existing or future).
- Optimize the control policy.

Processes: Routes of transmission

The main known routes for farm to farm transmission of the considered livestock diseases are (depending on the disease):

- Airborne spread.
- Movement of infected domestic animals.
- Movement of people: yatrogenic, farmers, etc.
- Contaminated fomites: vehicles, semen, material, etc.
- Infected food: meat, milk, cereals, etc.
- Infected wild animals: boars, deers, etc..
- Parasites: ticks, etc.

We also simulate the within farm transmission process with a SI model (ODE) $\Longrightarrow$ number of infected animals in each farm to compute dynamic coefficients.

Processes: Control measures

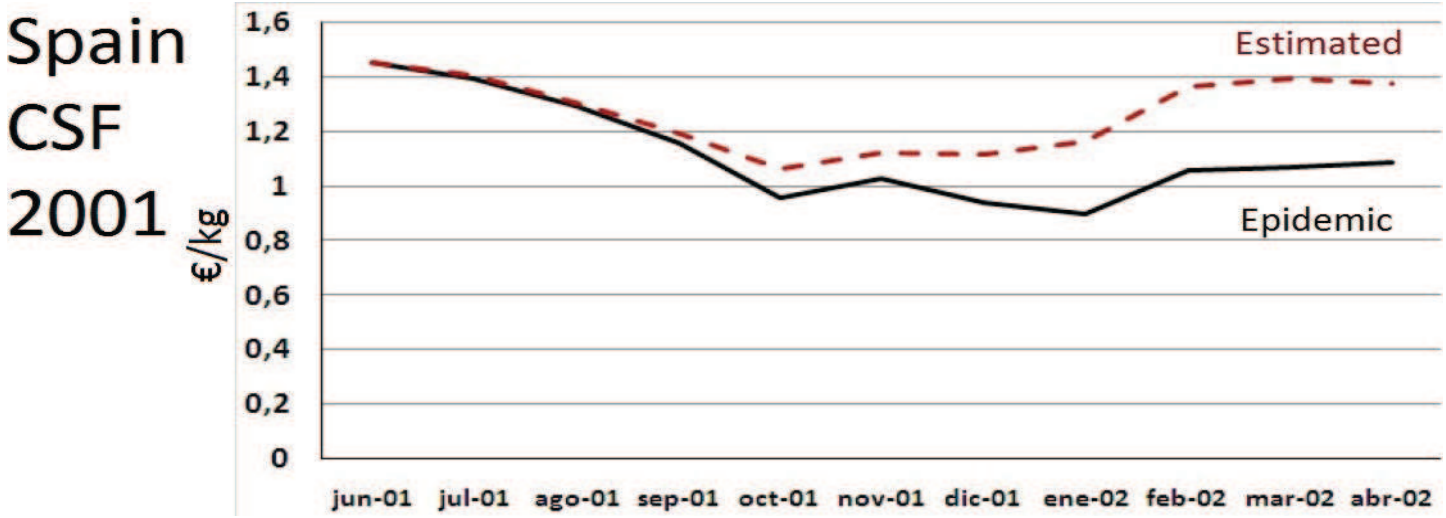
Depending on the considered area legislation, the measures to control and eradicate disease epidemics are based on:

- Culling.
- Zoning.
- Restrictions of movements.
- Increase of general surveillance: diagnostic tests, media campaigns, etc.
- Tracing.
- Vaccination.

Processes: Economical impact

Economical costs due to disease epidemics are classified as:

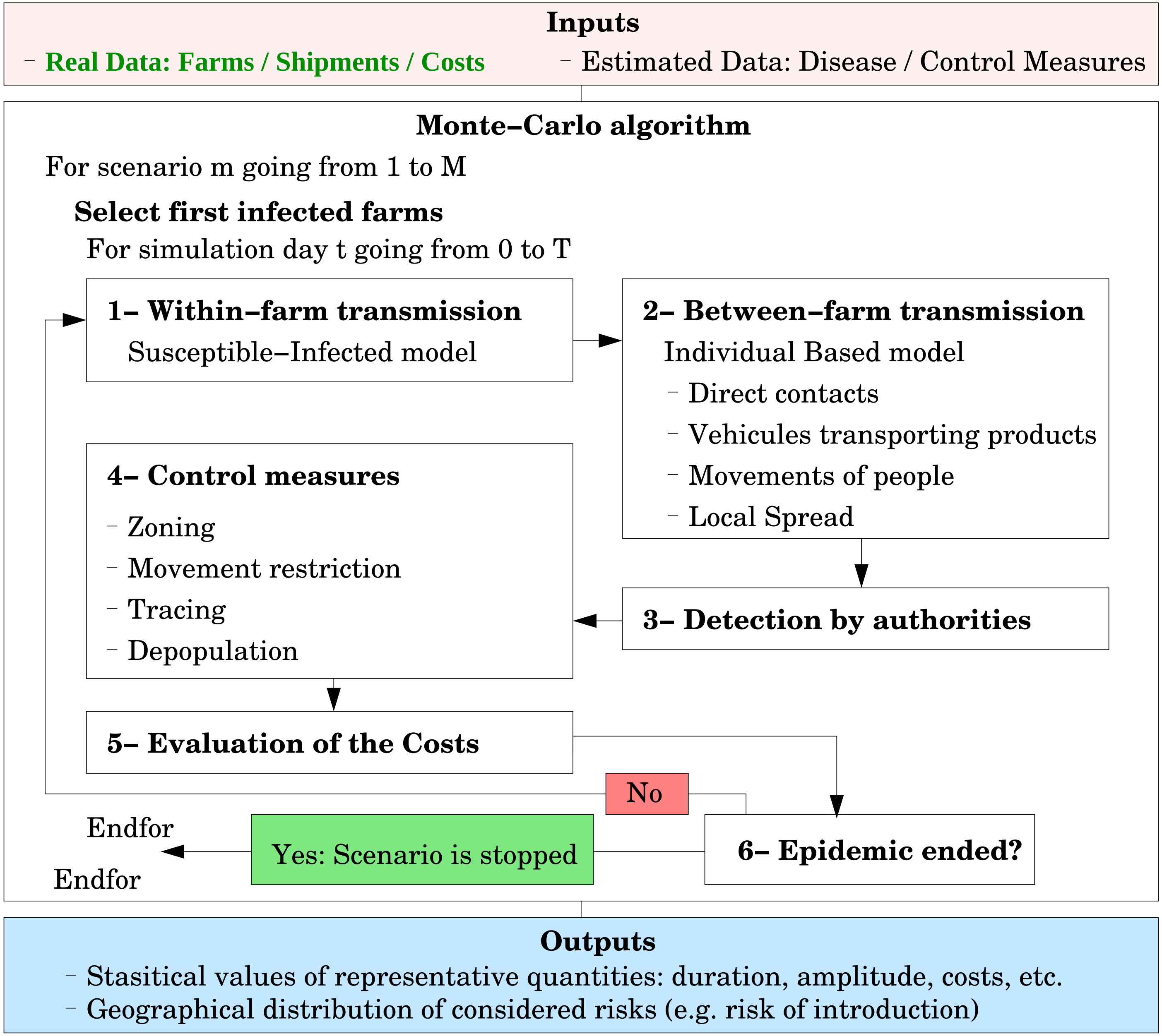
- Indirect: assumed by third-parties (farms, insurance companies, etc.) due to meat price devaluation.



- Transferable: paid by authorities due to control measures.
- Payable: paid by authorities to compensate third-parties.
- Computable: assumed by third-parties until the regularization of the situation (e.g., quarantine, productivity, etc.).

Example: CSF, Spain (4rd Pig Producer, 4.500 M€/yr), 2001, duration of 1 year, 49 outbreaks, estimated total cost 48 M€.

Structure of Be-FAST



Within-farm transmission

The within spread of a particular farm i is modeled using a stochastic 'Susceptible-Infected' model.

More precisely:

Pigs are characterized in two states: susceptible and infected.

The daily evolution $S_i(t)$ and $I_i(t)$ of the number of susceptible and infected pigs at farm i at day t, is governed by:

$$S_i(t+1) = S_i(t) - P(t),$$
$$I_i(t+1) = I_i(t) + P(t),$$

where $P(t)$ follows Poisson$(\beta_I \frac{S_i(t)I_i(t)}{S_i(t)+I_i(t)})$ and β_I is a suitable effective contact rate.

Between-farm transmission

The Between-farm disease transmission is modeled using a stochastic 'Individual Based' model:

Farms are characterized in four states: susceptible (S_H), infected (I_H), infectious (F_H) and clinical signs (C_H).

The order of transition from a state to the other is:

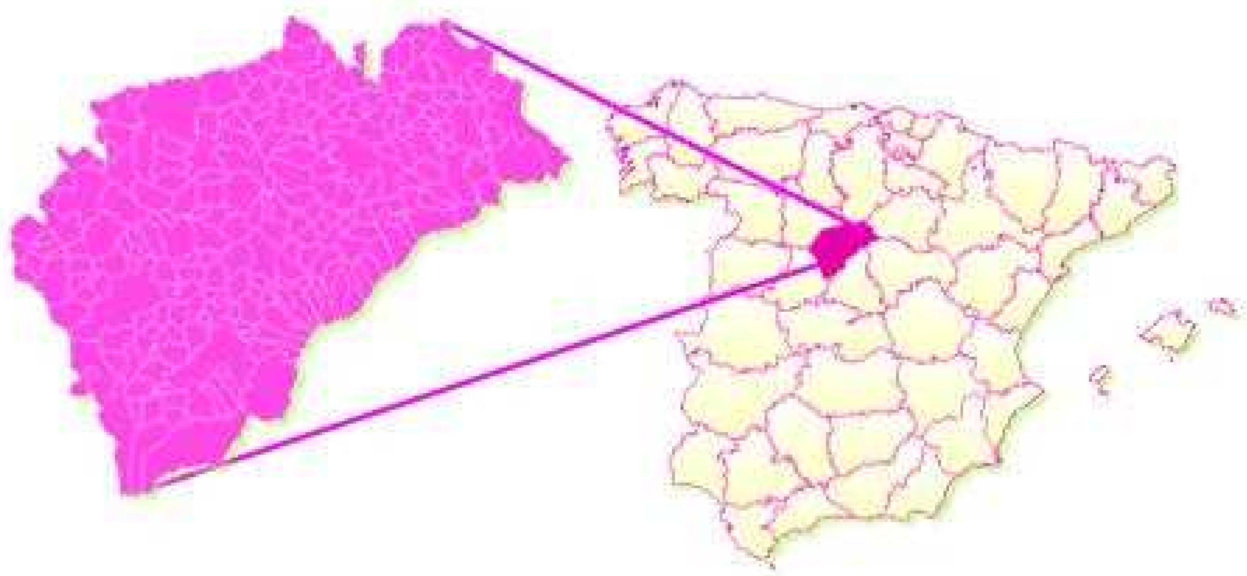
$$S_H \rightarrow I_H \rightarrow F_H \rightarrow C_H$$

Example of considered stochastic processes:

- Local spread: The daily probability of transmission between a farm i in the proximity of an infected farm j follows Bernoulli with mean depending on $I_j(t)$ and their distance.
- Tracing: Trace the contacts of a detected farm TR$\in \mathbb{N}$ days before detection. The probability of tracing movements and the probability of detection per day follow Bernoulli with fixed mean.

CSF in Segovia: Case description

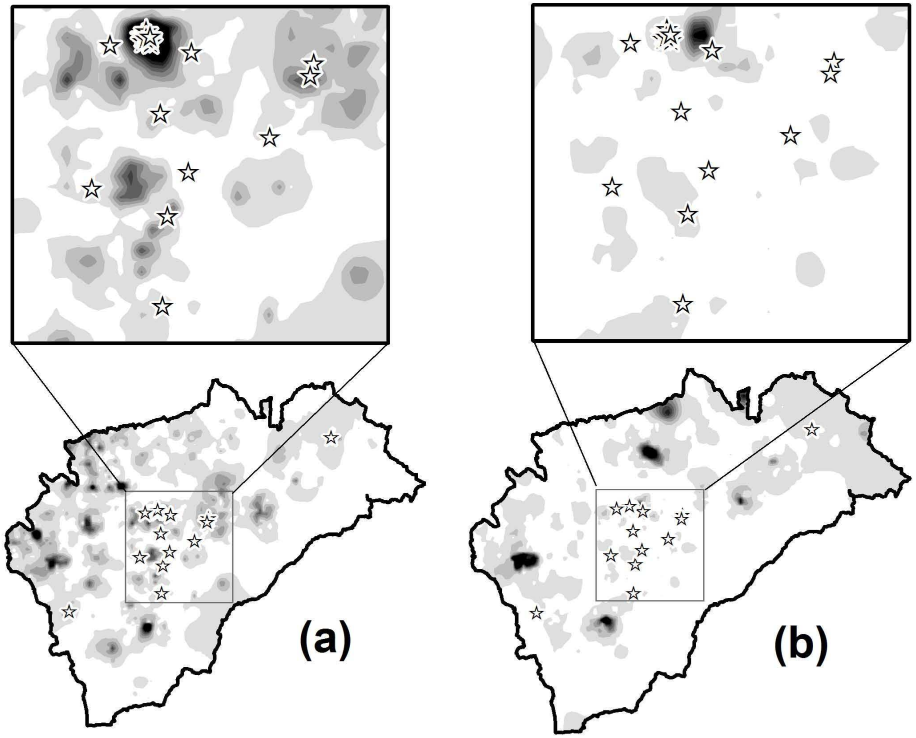
We consider the Spanish region of Segovia (important areas of pig production).



Data of the region: Surface of 6796 km^2, 1400 pig farms, 1.400.000 pigs.
Data from Real Epidemic: 1997-98, 58 infected farms, epidemic duration of 60 days, cost of 36 M€.
Experiments: Model validation. Comparison with InterSpread.

CSF in Segovia: Some results

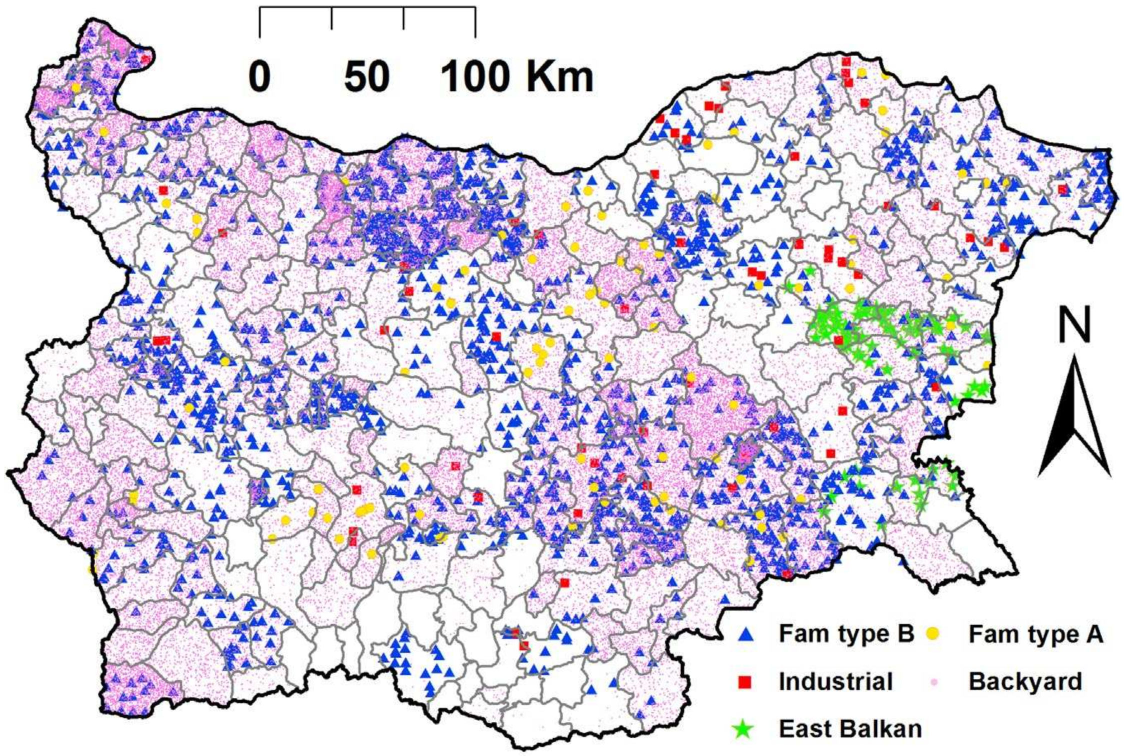
Model	Comp. Time (s)	% cause of infection			
		LOC	*INT*	*SDA*	*TRA*
Be-FAST	9400	54	26	14	6
IS	11000	51	13	10	26
REAL	-	52	24	20	4



Estimated Simulated Cost: 35 M€(vs. 36 M€).

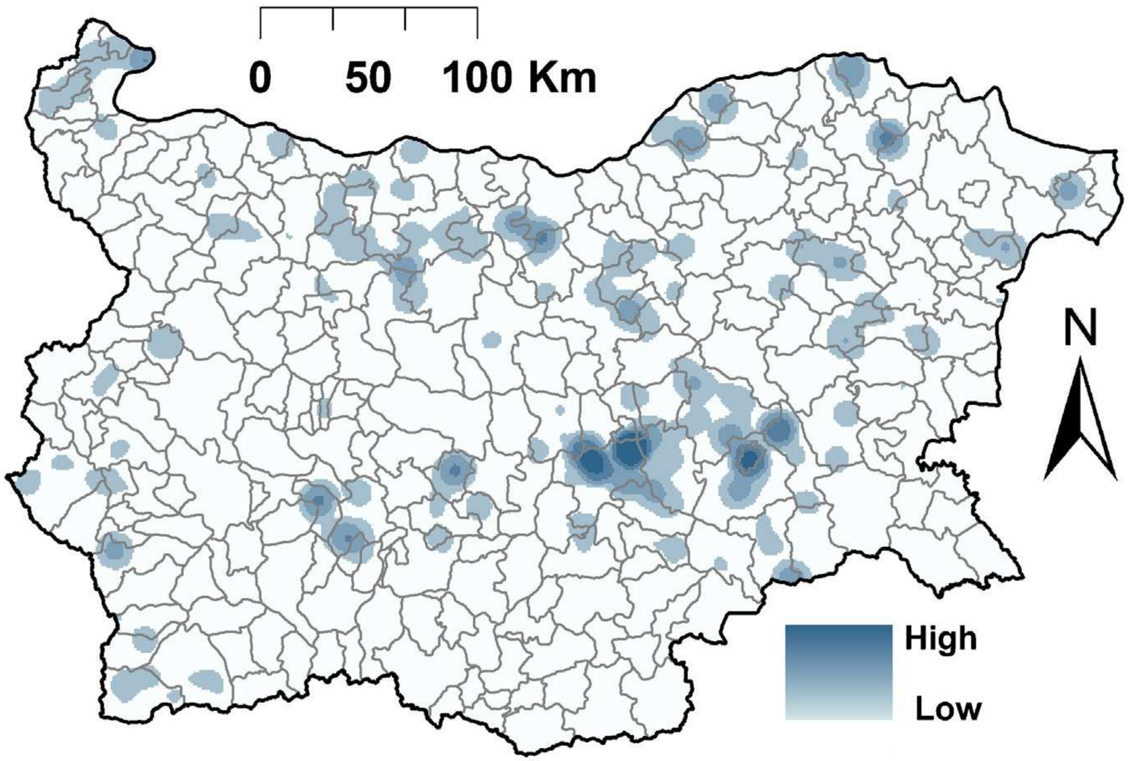
CSF in Bulgaria: Case description

We consider Bulgaria:



Data of the region: Surface of 110.994 km^2, 64.000 pig farms, 600.000 pigs.
Experiments: Study the Risk of CSF spread (RS) due to Backyard farms (assumed high).

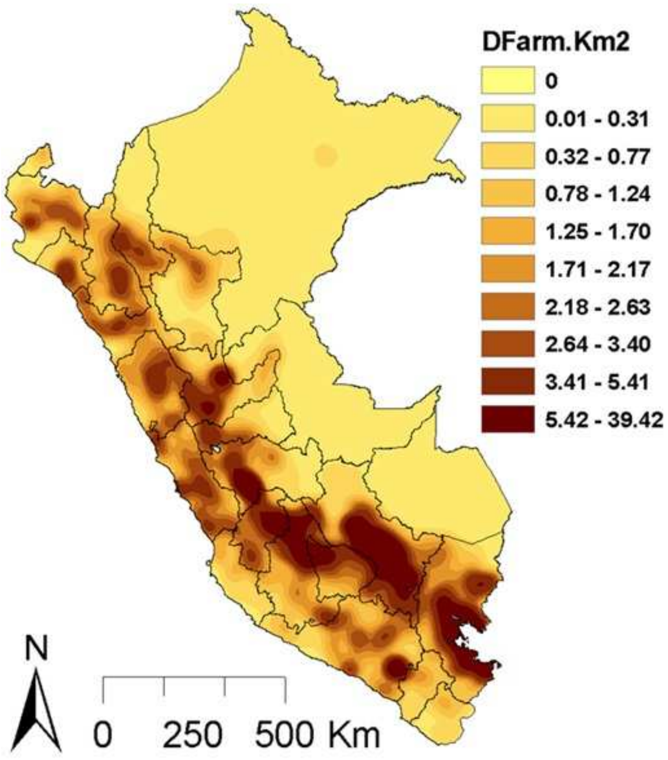
CSF in Bulgaria: Some Results



Farm Type	Industrial	A/B	Backyard	East Balkan
% of inf.	56.1	20.3	13.2	10.4
Risk of Spread	7.5	1	1	1

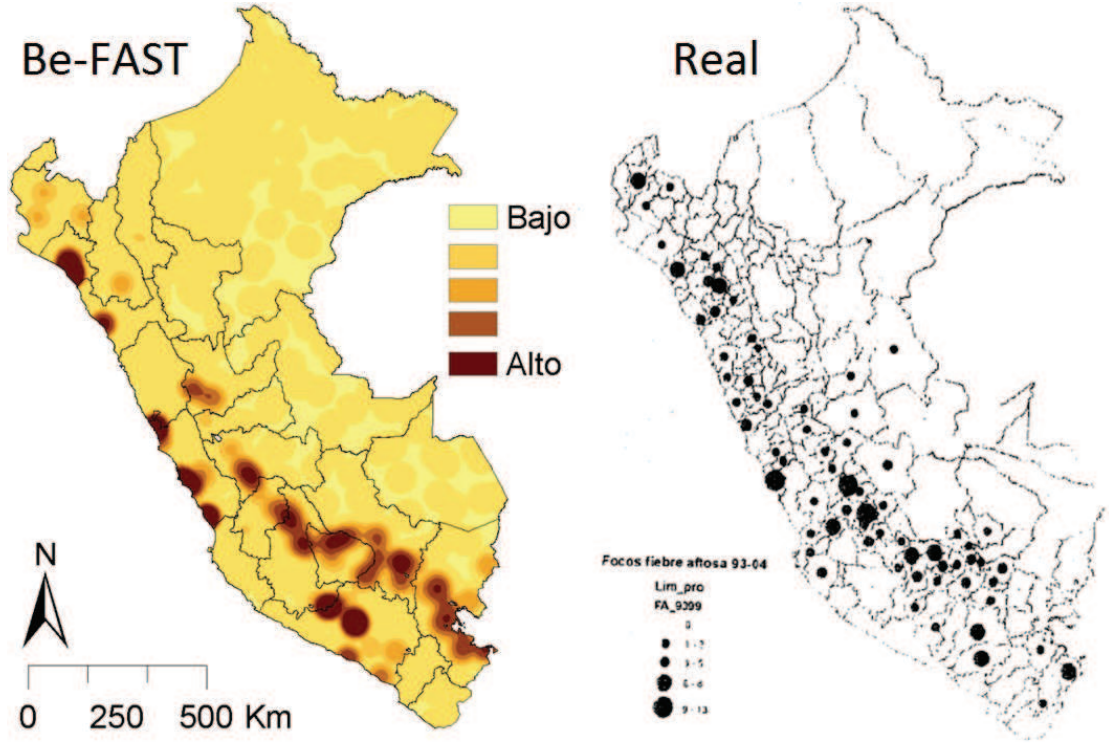
FMD in Peru: Case description

We consider Peru:



Data of the region: Surface of 1.285.216 km^2, 2.000.000 farms, 15.240.348 animals. Real epidemic data (OEI).
Experiments: Study the Risk of FMD spread. Evaluate the amplitude of culling and restrictions in the worst scenarios.

FMD in Peru: Some Results

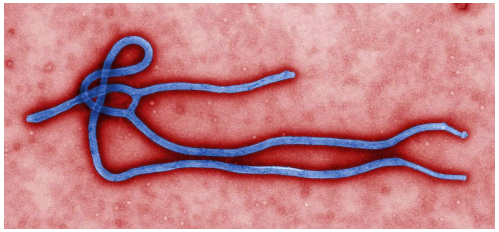


Culled farms	770
Culled animals	9.500
Restricted farms	500.000
Restricted animals	3.000.000
Epidemic length	260

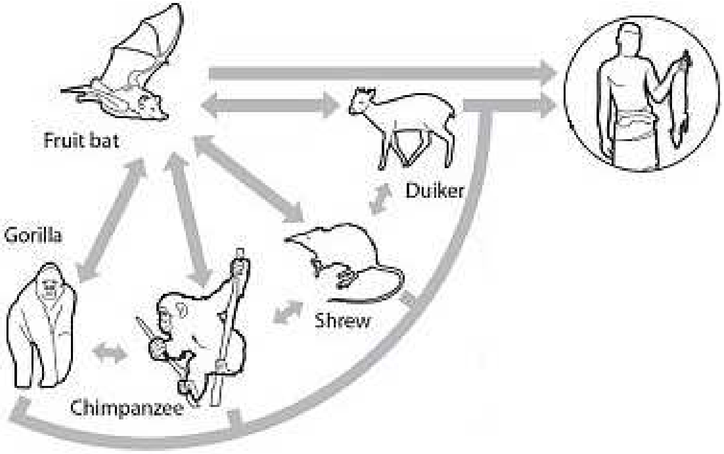
Part III: Be-CoDiS model

Ebola Virus Disease

- Ebola Virus Disease (EDV) is a lethal (between [25%,90%]) human and primates virus disease that causes important clinical signs (i.e., haemorrhages, fever or muscle pain).

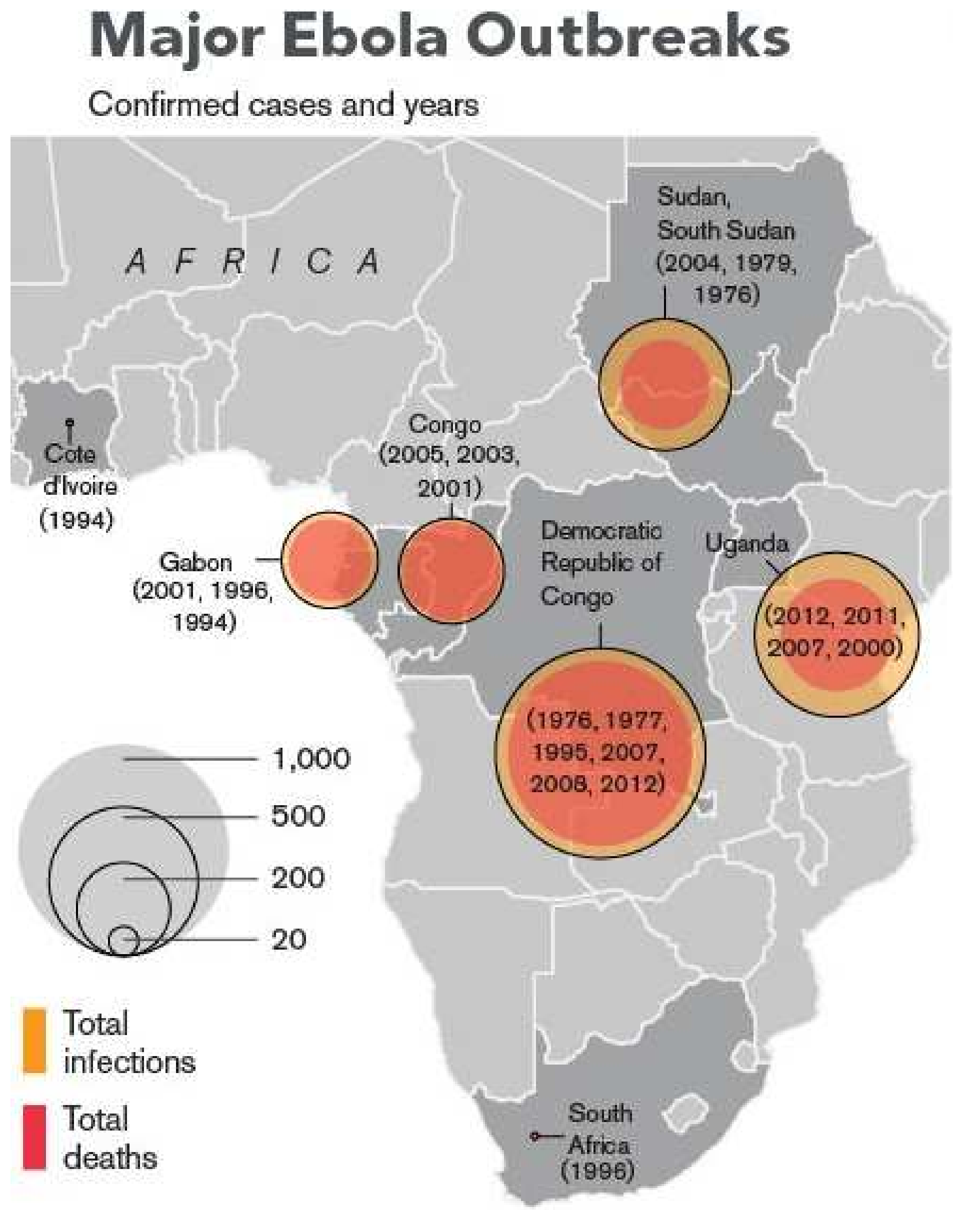


- Bats are the main known reservoir:

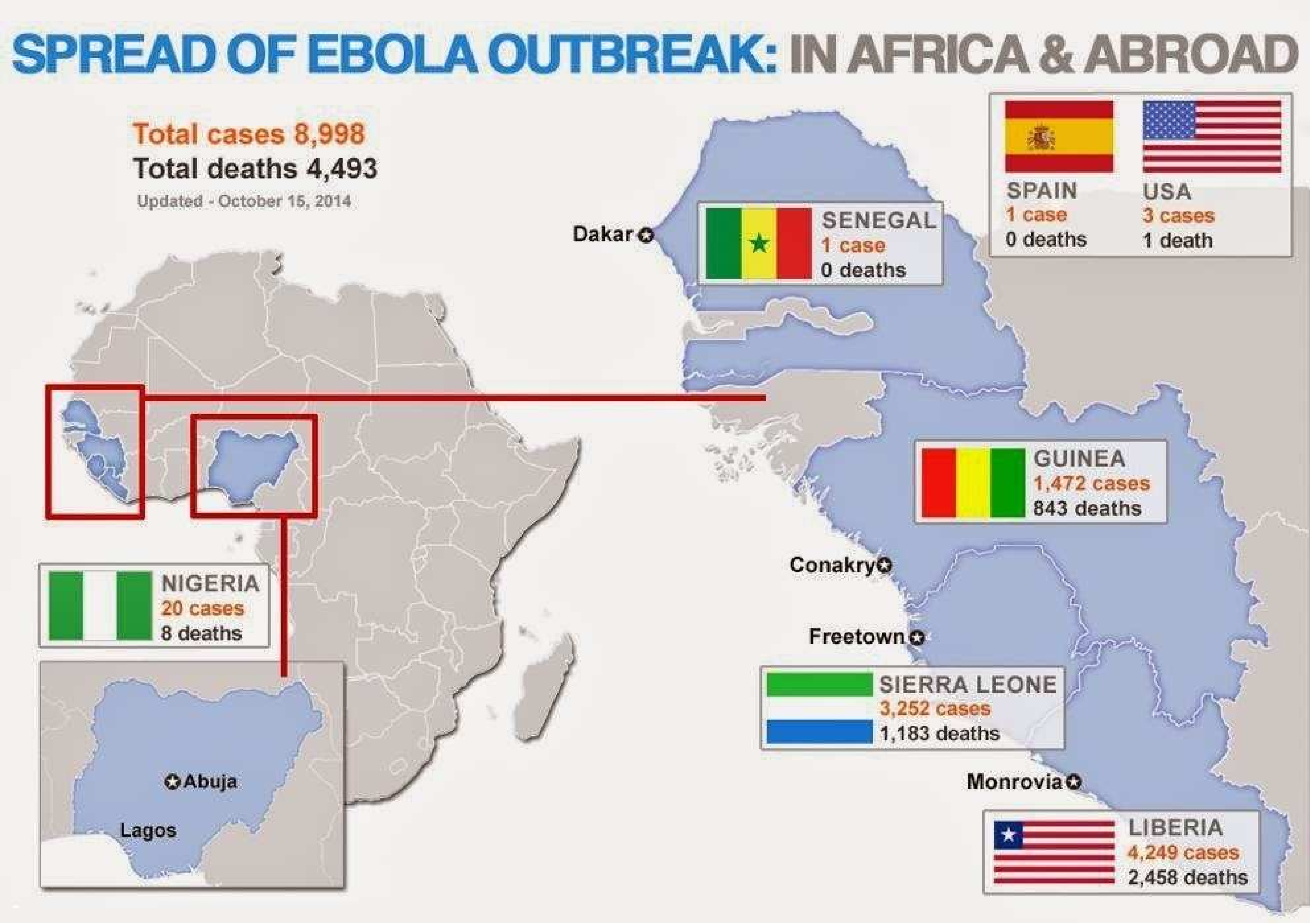


- The principal route of human transmission are the contacts with infected fluids or fomites.

Historical situation



The 2014 epidemic situation: 15/10/2014



The 2014 epidemic situation: Some key dates

- December, 2013 - Guinea: Index case identified as boy died of EDV in the village of Meliandou. Its familiy is infected. Source of infection: bushmeat of bats.
- March, 2014 - Guinea: World Health Organization reported major EDV outbreak (86 cases / 59 deaths). Beginning of extensive control measures.
- March, 2014 - Liberia: First reported EDV cases.
- June, 2014 - Sierra-Leone: First reported EDV cases.
- August, 2014 - Liberia and Sierra Leone: Applications of strict control measures.
- November, 2014: Cumulative cases/deaths: Guinea: 1667 (1018) — Liberia: 6535 (2413) — Sierra Leone: 5338 (1510) — Nigeria: 20 (8) — Sporadic Cases (<10): Mali, Senegal, USA, Spain.

Ebola Virus Disease Characteristics

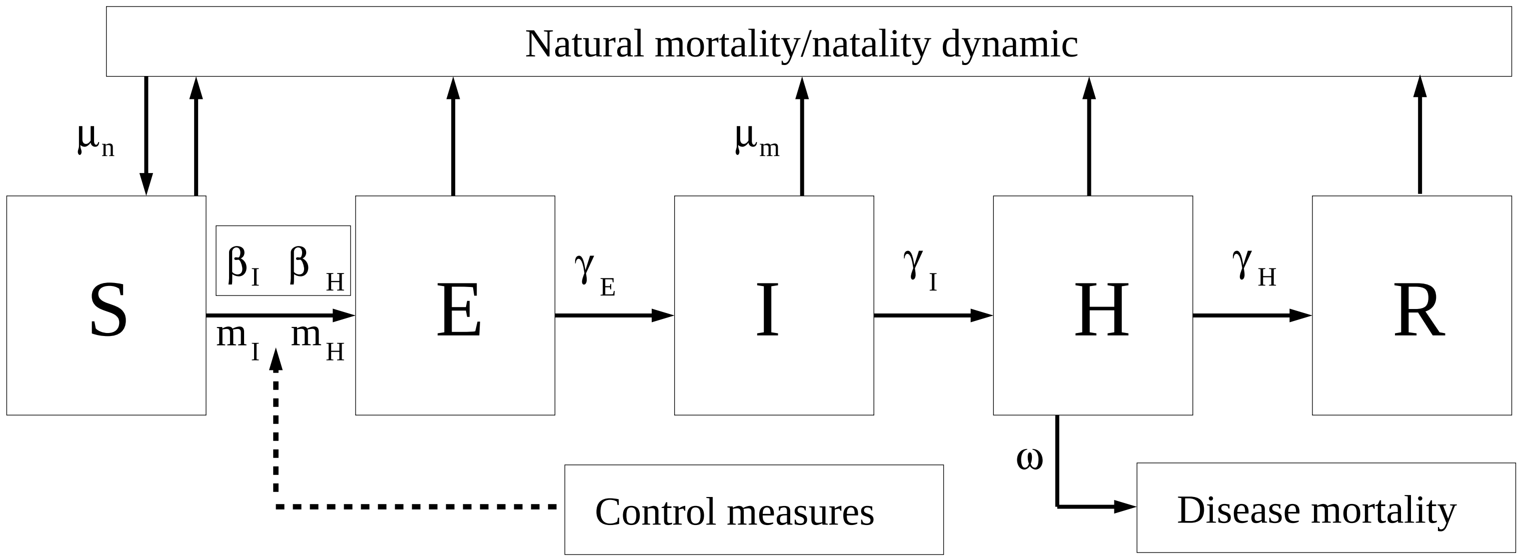
Considering data from the current epidemic:

Sates of an infected persons:

- Infected (E): Infected persons in latent period that cannot infect other persons. Duration: 11.4 [2,21] days.
- Infectious (I): Can infect other people and start developing clinical signs. Duration: 5.3 days [1,10] days).
- Hospitalized (H): Can still infect other people but with a 38 times lower probability. The mean duration of an hospitalization is 6.4 days [1,18] days. EDV mortality mainly occurs at this stage (around 70.8%.).
- Recovered (R): The person is recovered from the epidemic and is immune.
- Control measures: Isolation of infected persons, Quarantine of affected areas and Tracing.

Within-country spread: Flow diagram

Inside a country the evolution of number of persons in each EDV states is given by the considered flow:



Regarding control measures, we consider:

$$m_I(t) = m_H(t) = \exp\Big(-\kappa \max(t-\lambda, 0)\Big),$$

Within-country spread: System

$$
\begin{aligned}
\frac{\mathrm{d}S(t)}{\mathrm{d}t} &= -\frac{S(t)\Big(m_I(t)\beta_I(t)I(t)+m_H(t)\beta_H(t)H(t)\Big)}{NP(t)} \\
&\quad +\mu_n\Big(S(t)+E(t)+I(t)+H(t)+R(t)\Big)-\mu_m S(t), \\
\frac{\mathrm{d}E(t)}{\mathrm{d}t} &= \frac{S(t)\Big(m_I(t)\beta_I(t)I(t)+m_H(t)\beta_H(t)H(t)\Big)}{NP(t)} \\
&\quad -(\mu_m+\gamma_E)E(t), \\
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= \gamma_E E(t)-(\mu_m+\gamma_I)I(t), \\
\frac{\mathrm{d}H(t)}{\mathrm{d}t} &= \gamma_I I(t)-(\mu_m+\gamma_H)H(t), \\
\frac{\mathrm{d}R(t)}{\mathrm{d}t} &= (1-\omega)\gamma_H H(t)-\mu_m R(t),
\end{aligned}
$$

Within-country spread: Parameters estimation

Main data source: Example for 31^{Th}October, 2014:
http://www.who.int/csr/disease/ebola/situation-reports/en/

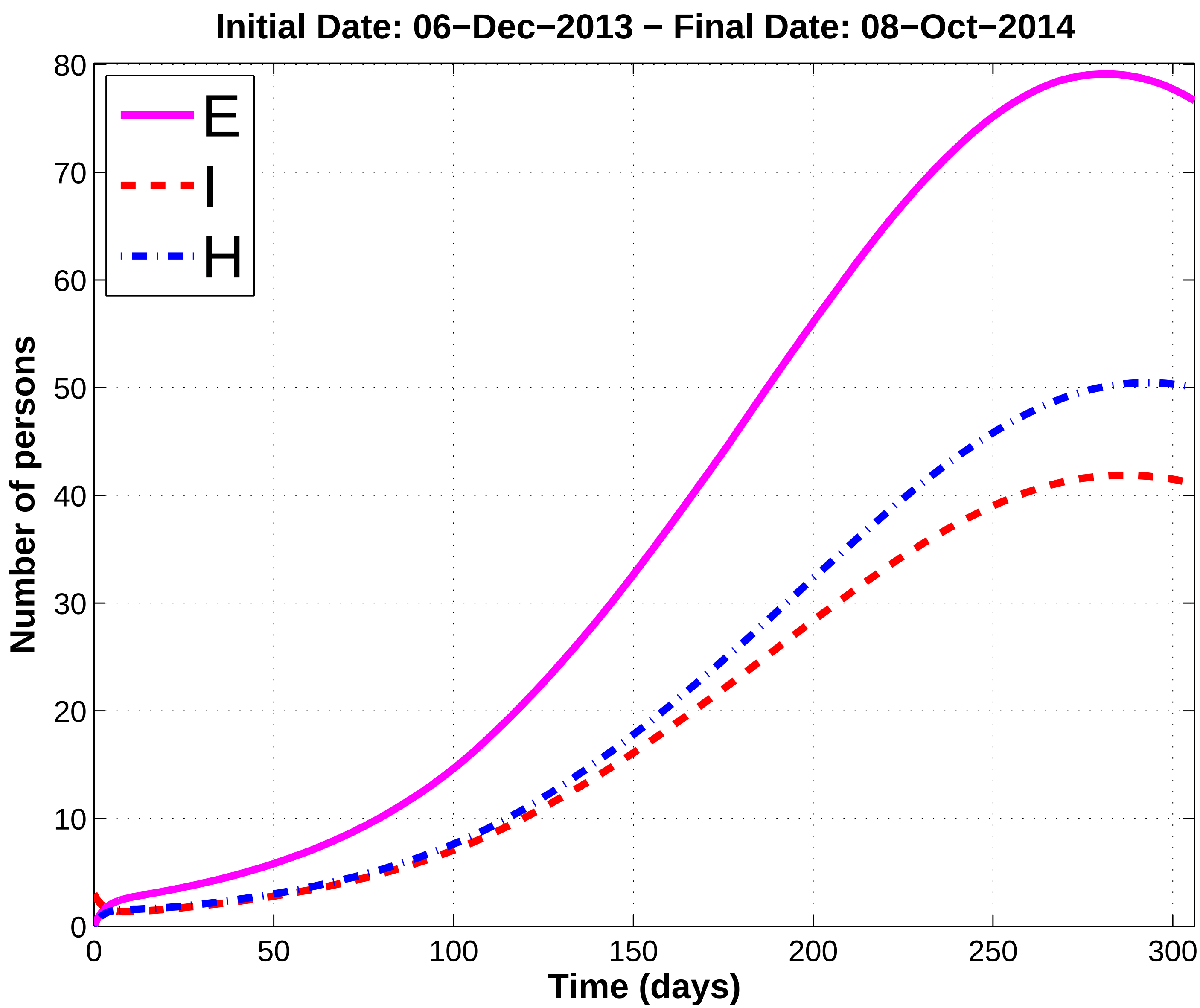
Table 1: Confirmed, probable, and suspected cases in Guinea, Liberia, and Sierra Leone

Country	Case definition	Cumulative Cases	Deaths
Guinea	Confirmed	1409	*
	Probable	204	*
	Suspected	54	*
	All	**1667**	**1018**
Liberia	Confirmed	2515	*
	Probable	1540	*
	Suspected	2480	*
	All	**6535**	**2413**
Sierra Leone	Confirmed	3778	*
	Probable	322	*
	Suspected	1238	*
	All	**5338**	**1510**
Total		**13 540**	**4941**

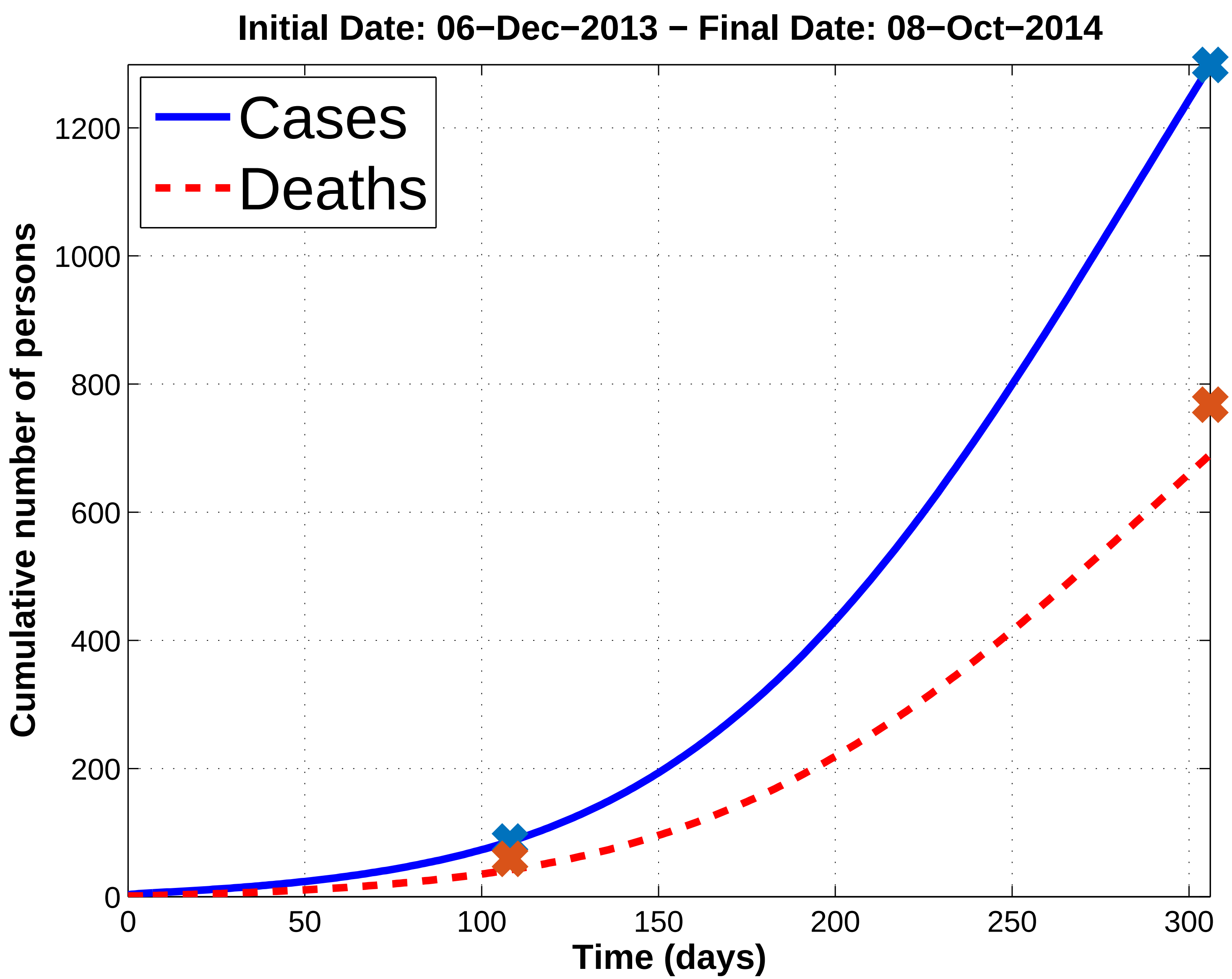
**N/A. Data are based on official information reported by Ministries of Health. These numbers are subject to change due to ongoing reclassification, retrospective investigation and availability of laboratory results.*

Regression and fitting techniques for evaluating unknown parameters.

Within-country spread: Example of Guinea



Within-country spread: Example of Guinea



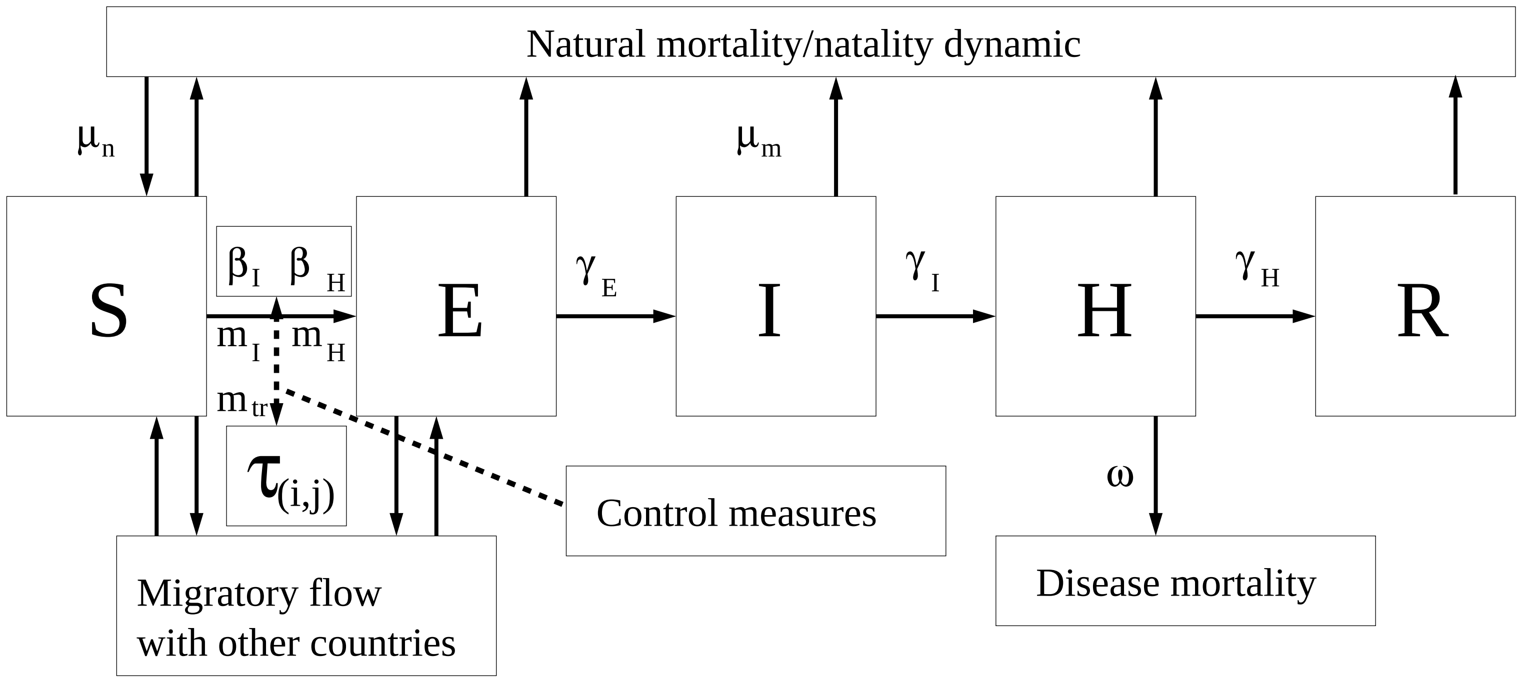
Between-countries spread: Global migration data

Partnership
Outline
Part I: A short introduction to epidemiology
Part II: Be-FAST model
Part III: Be-CoDiS model
Ebola Virus Disease
History
The 2014 epidemic
EDV States
Within-country spread
Between-country spread
Short term
Long term
Conclusions and perspectives

Source: Abel & Sander (2014). *Quantifying Global International Migration Flows.* **Science**, 343 (6178).

Between-countries spread: Flow diagram

The worldwide evolution of number of persons in each EDV states is given by the considered flow:



Regarding control measures, we consider:

$$m_I(i,t) = m_H(i,t) \text{ and } m_{\mathrm{tr}}(i,j,t) = m_I(i,t)m_I(j,t)$$

Between-countries spread: System

$$\frac{\mathrm{d}S(i,t)}{\mathrm{d}t} = -\frac{S(i,t)\Big(m_I(i,t)\beta_I(i,t)I(i,t)+m_H(i,t)\beta_H(i,t)H(i,t)\Big)}{NP(i,t)}$$
$$+\mu_n(i)\Big(S(i,t)+E(i,t)+I(i,t)+H(i,t)+R(i,t)\Big)-\mu_m(i)S(i,t)$$
$$+\sum_{i\neq j} m_{\mathrm{tr}}(i,j,t)\tau(j,i)S(j,t)-\sum_{i\neq j} m_{\mathrm{tr}}(i,j,t)\tau(i,j)S(i,t),$$

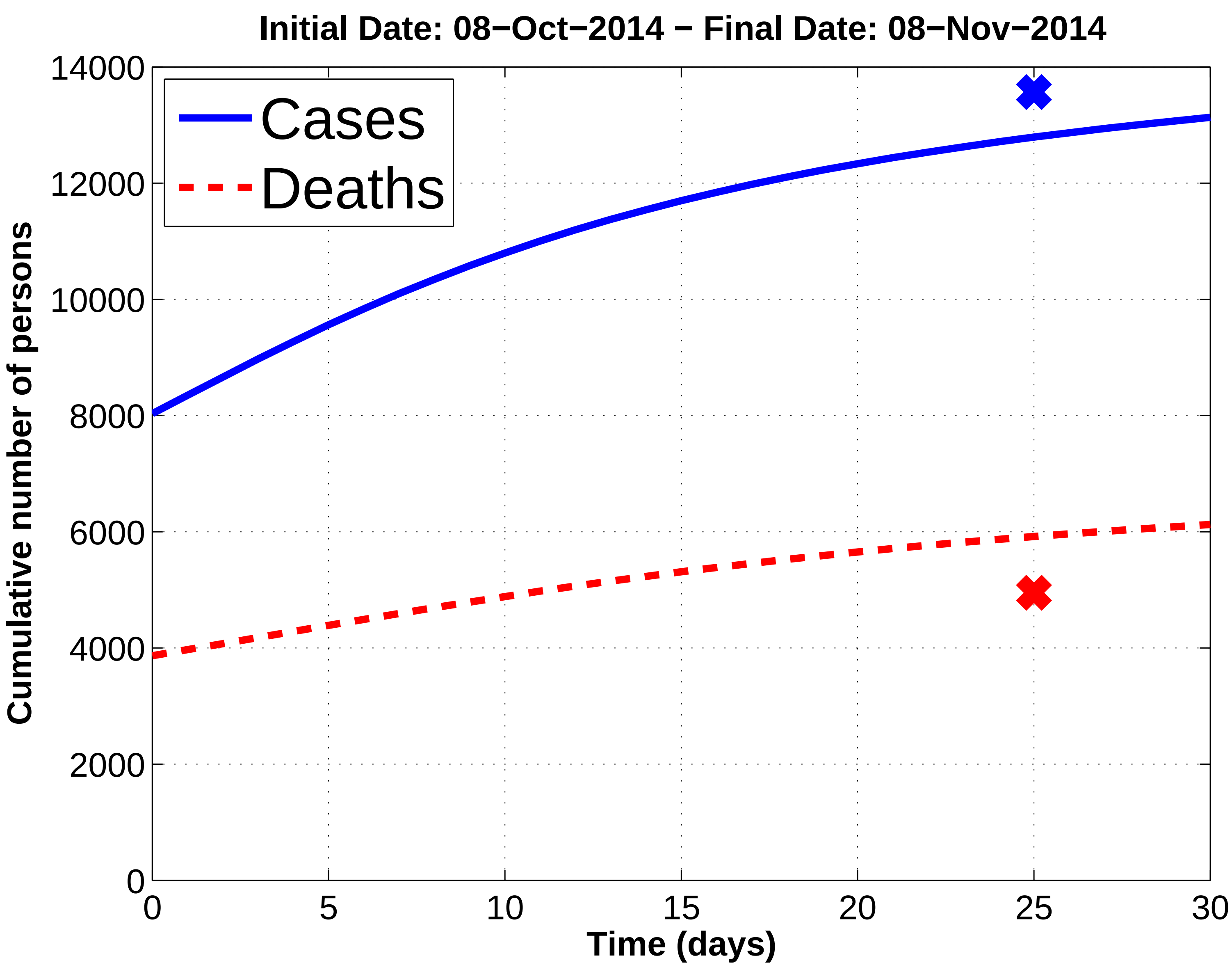
$$\frac{\mathrm{d}E(i,t)}{\mathrm{d}t} = \frac{S(i,t)\Big(m_I(i,t)\beta_I(i,t)I(i,t)+m_H(i,t)\beta_H(i,t)H(i,t)\Big)}{NP(i,t)}$$
$$+\sum_{i\neq j} m_{\mathrm{tr}}(i,j,t)\tau(j,i)E(j,t)-\sum_{i\neq j} m_{\mathrm{tr}}(i,j,t)\tau(i,j)E(i,t)$$
$$-(\mu_m(i)+\gamma_E)E(i,t),$$

$$\frac{\mathrm{d}I(i,t)}{\mathrm{d}t} = \gamma_E E(i,t)-(\mu_m(i)+\gamma_I)I(i,t),$$

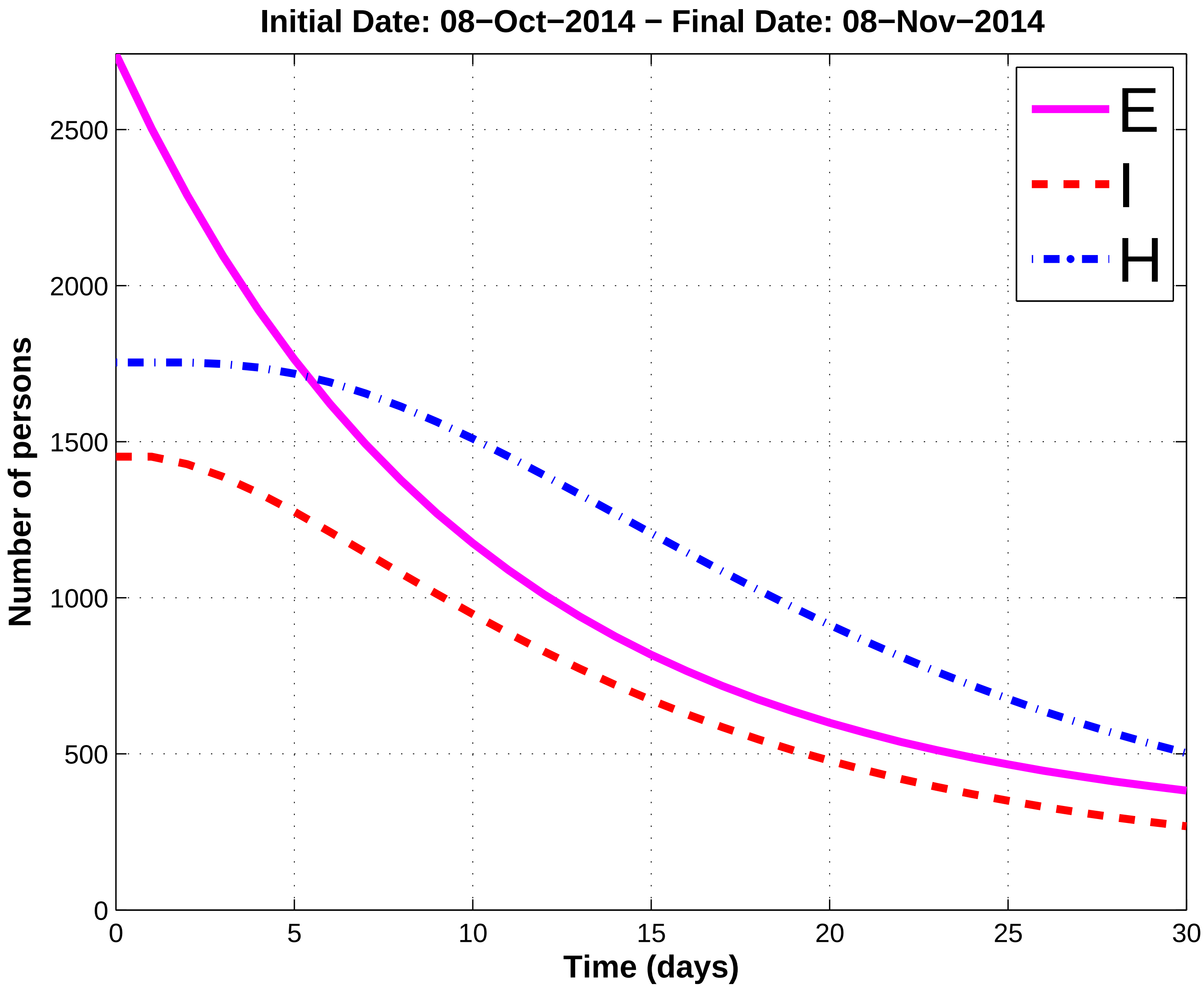
$$\frac{\mathrm{d}H(i,t)}{\mathrm{d}t} = \gamma_I I(i,t)-(\mu_m(i)+\gamma_H)H(i,t),$$

$$\frac{\mathrm{d}R(i,t)}{\mathrm{d}t} = (1-\omega(i))\gamma_H H(i,t)-\mu_m(i)R(i,t),$$

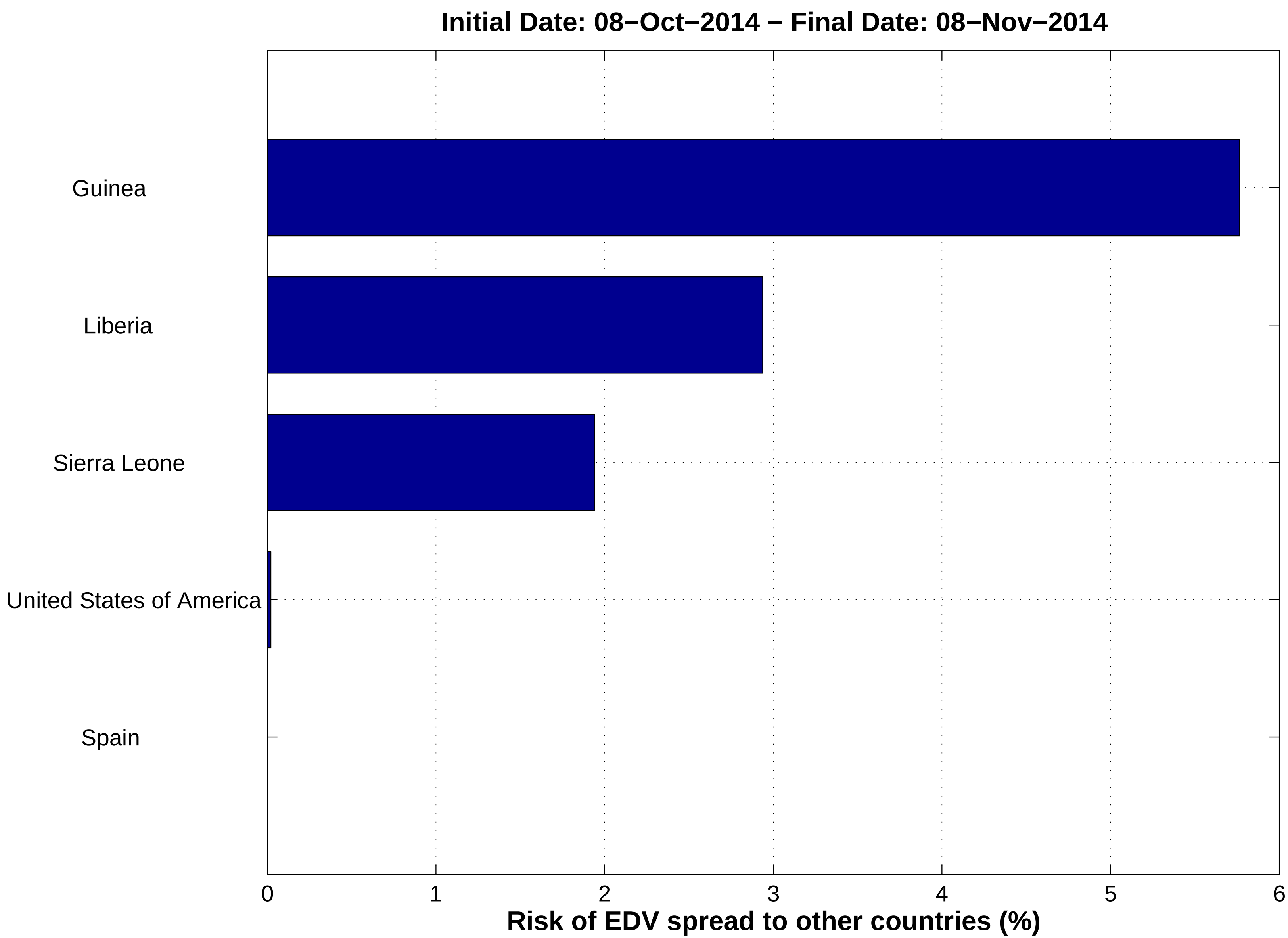
Application to EDV: Short term forecast



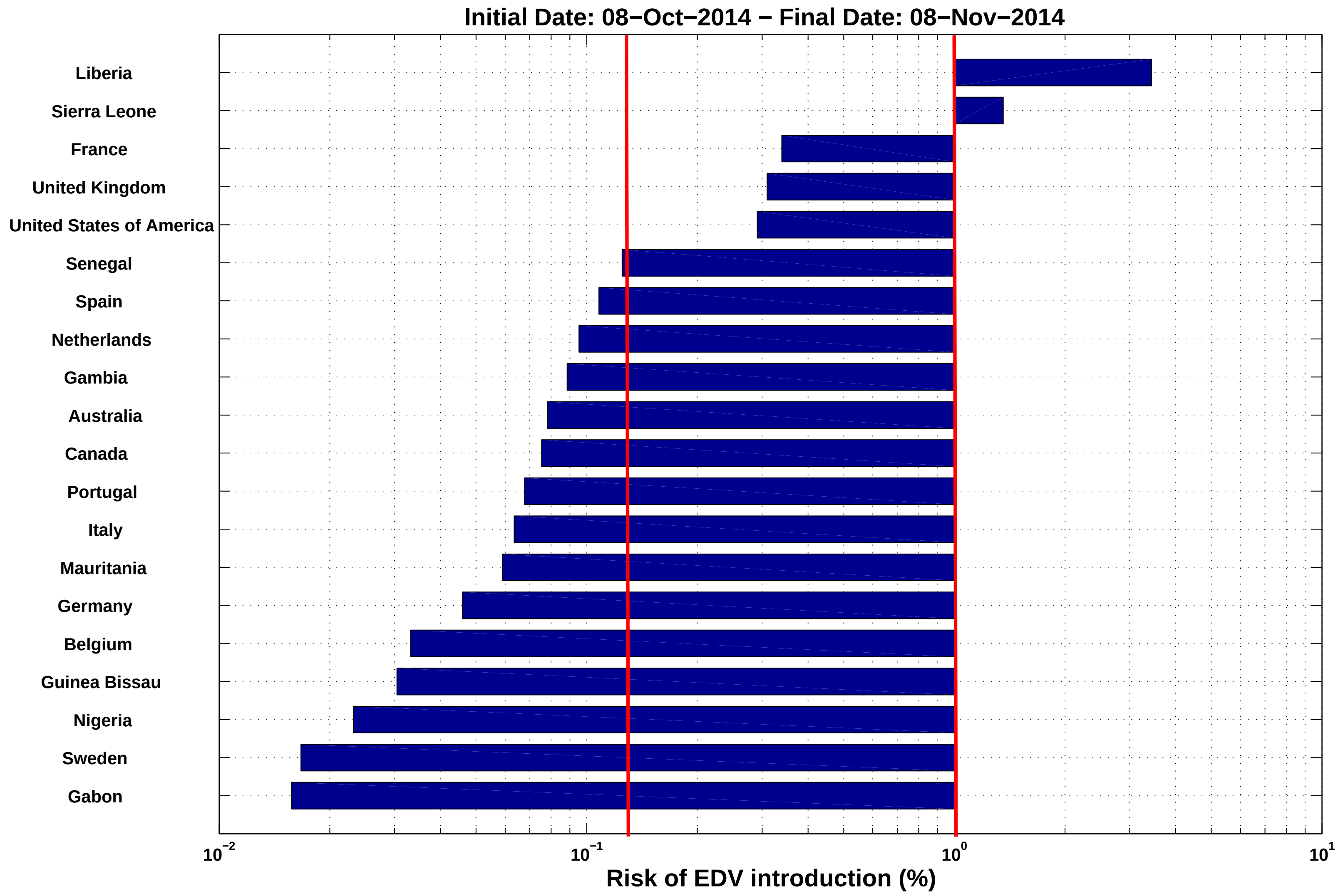
Application to EDV: Short term forecast



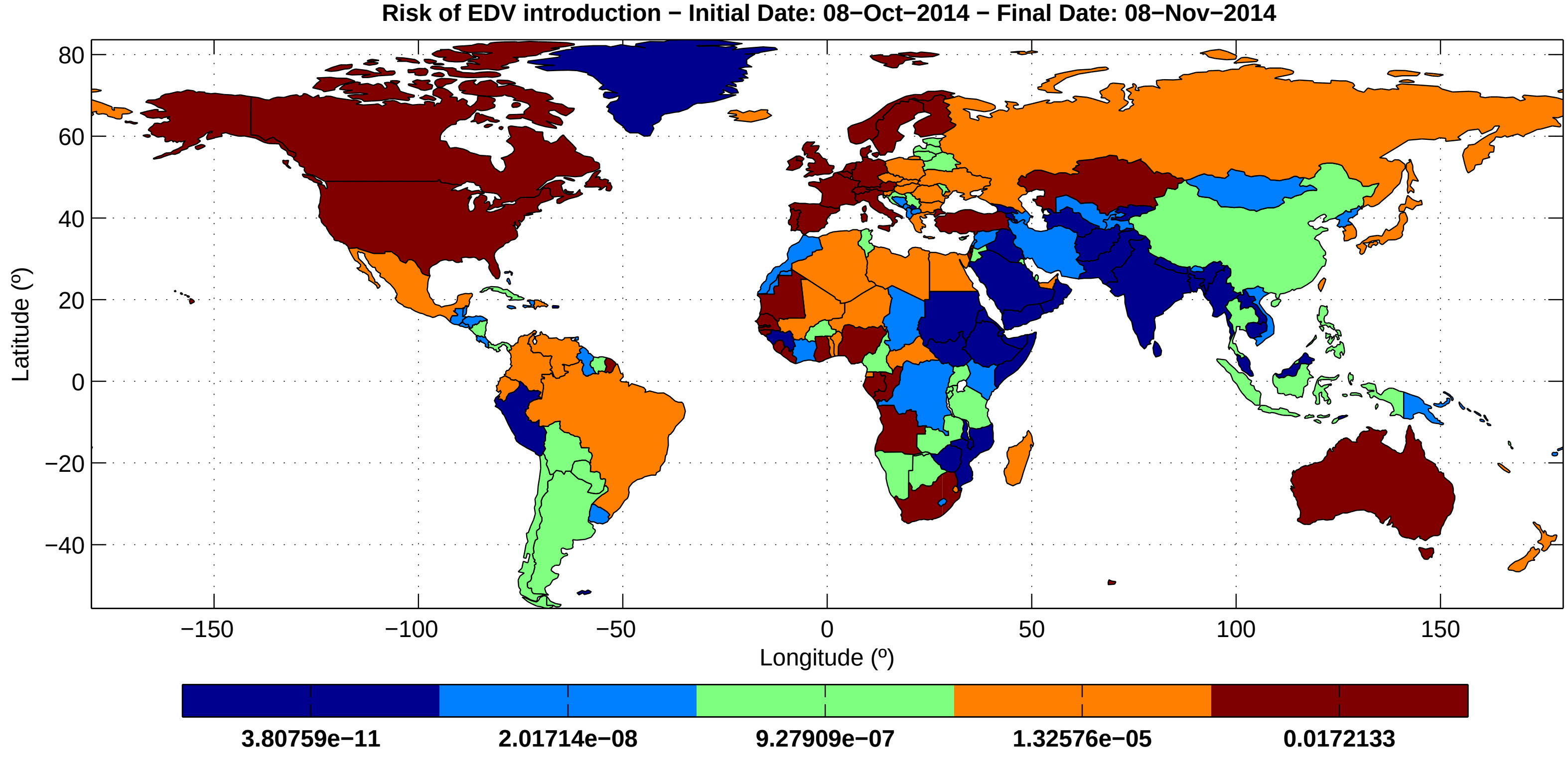
Application to EDV: Short term forecast



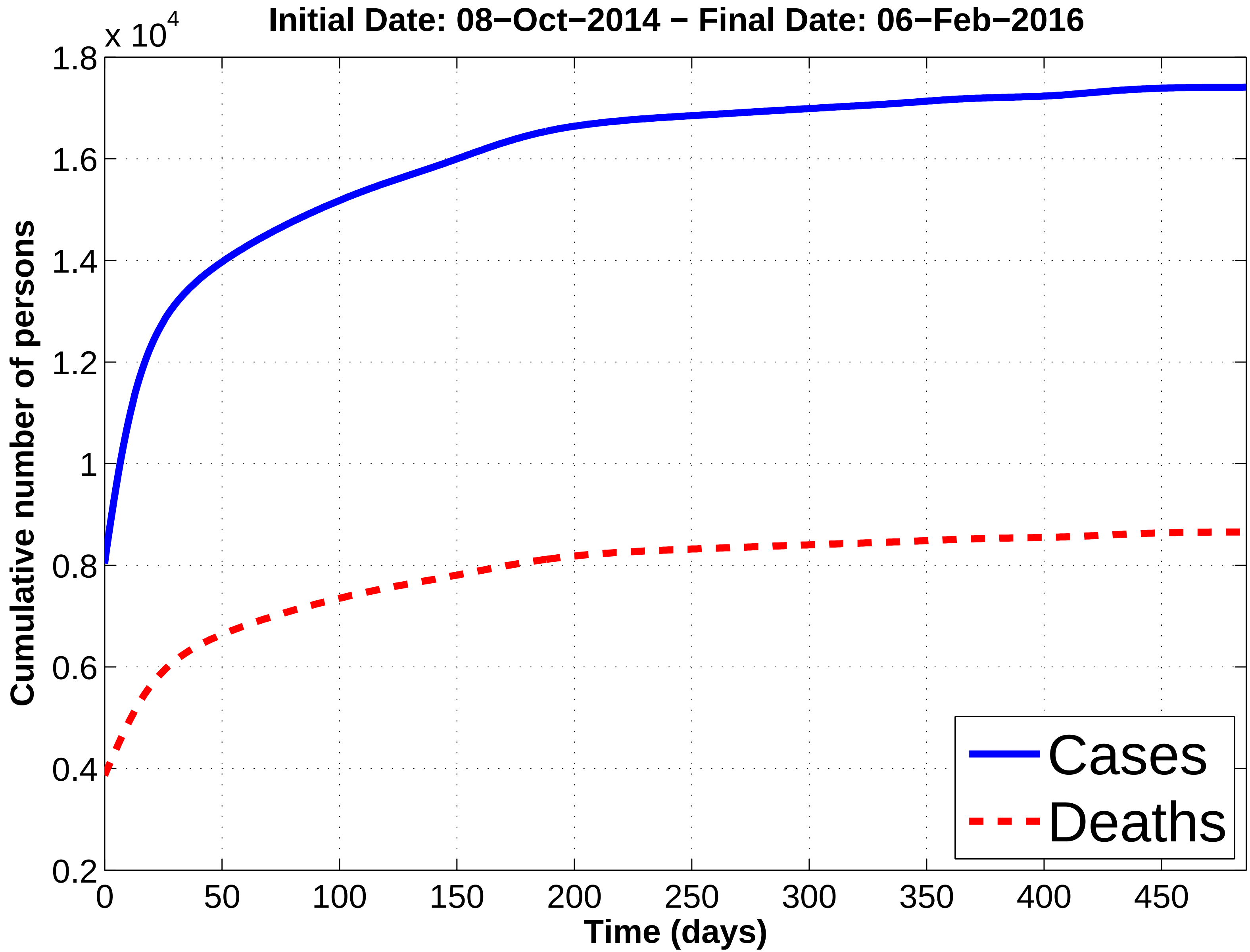
Application to EDV: Short term forecast



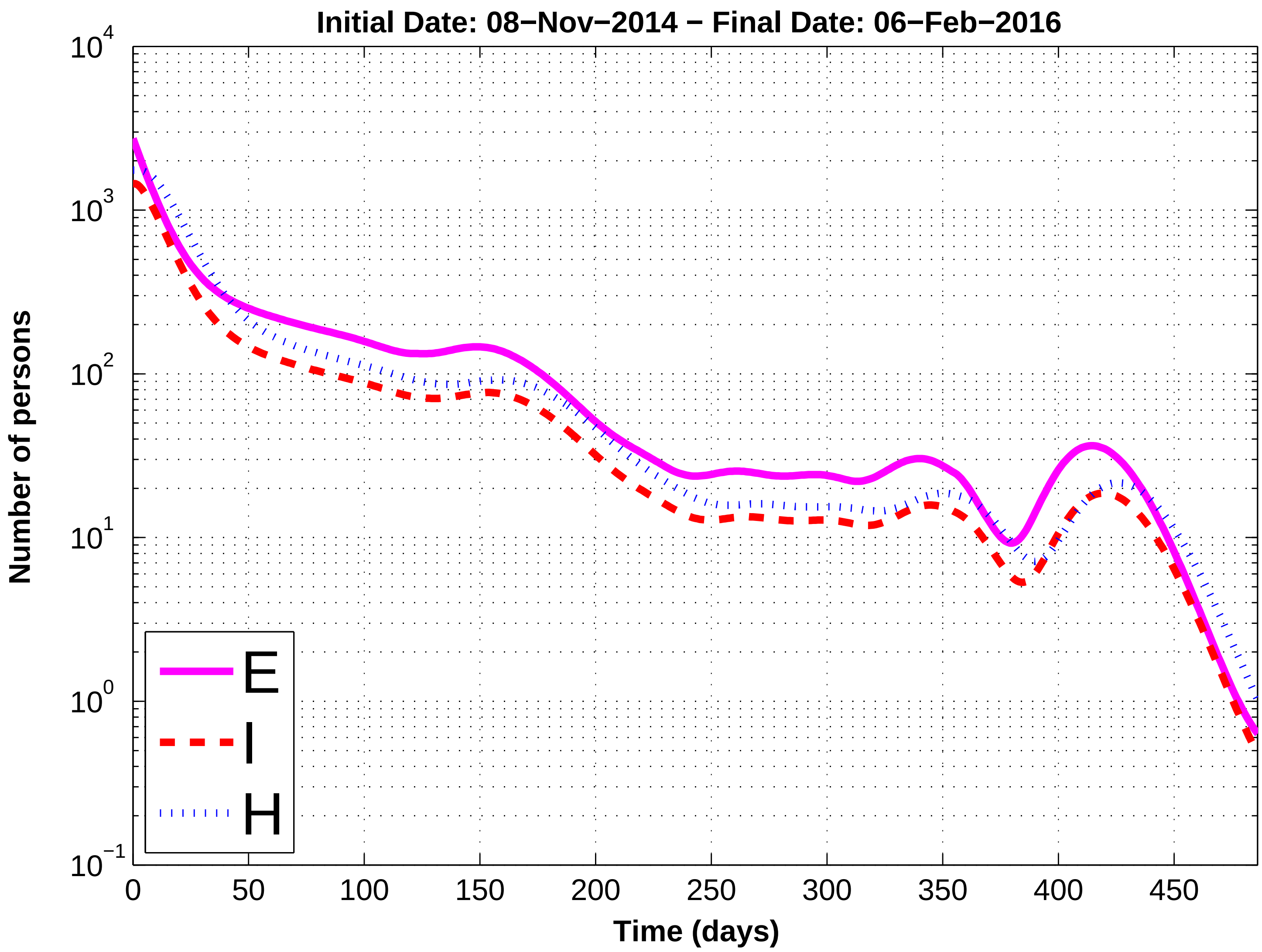
Application to EDV: Short term forecast



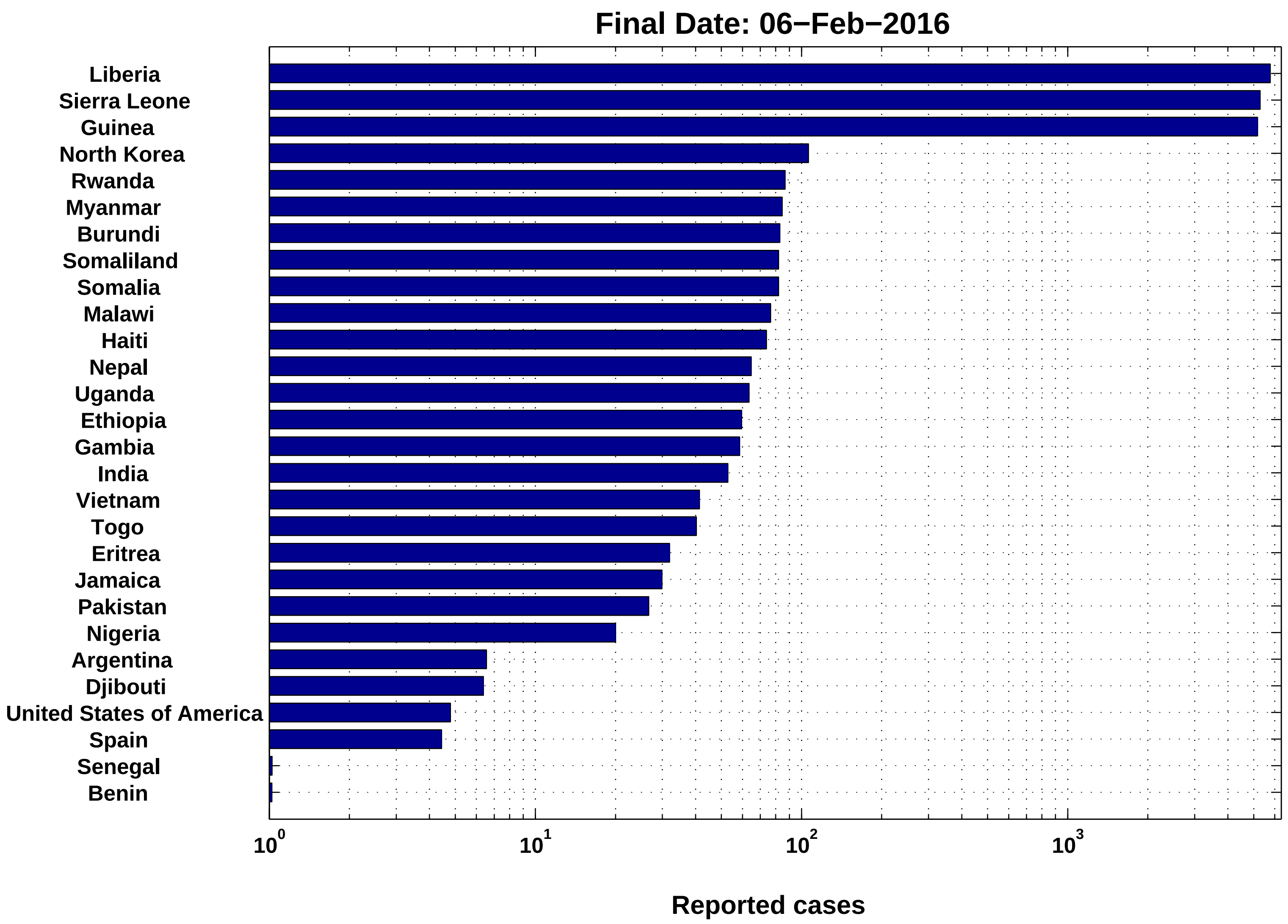
Application to EDV: Long term forecast



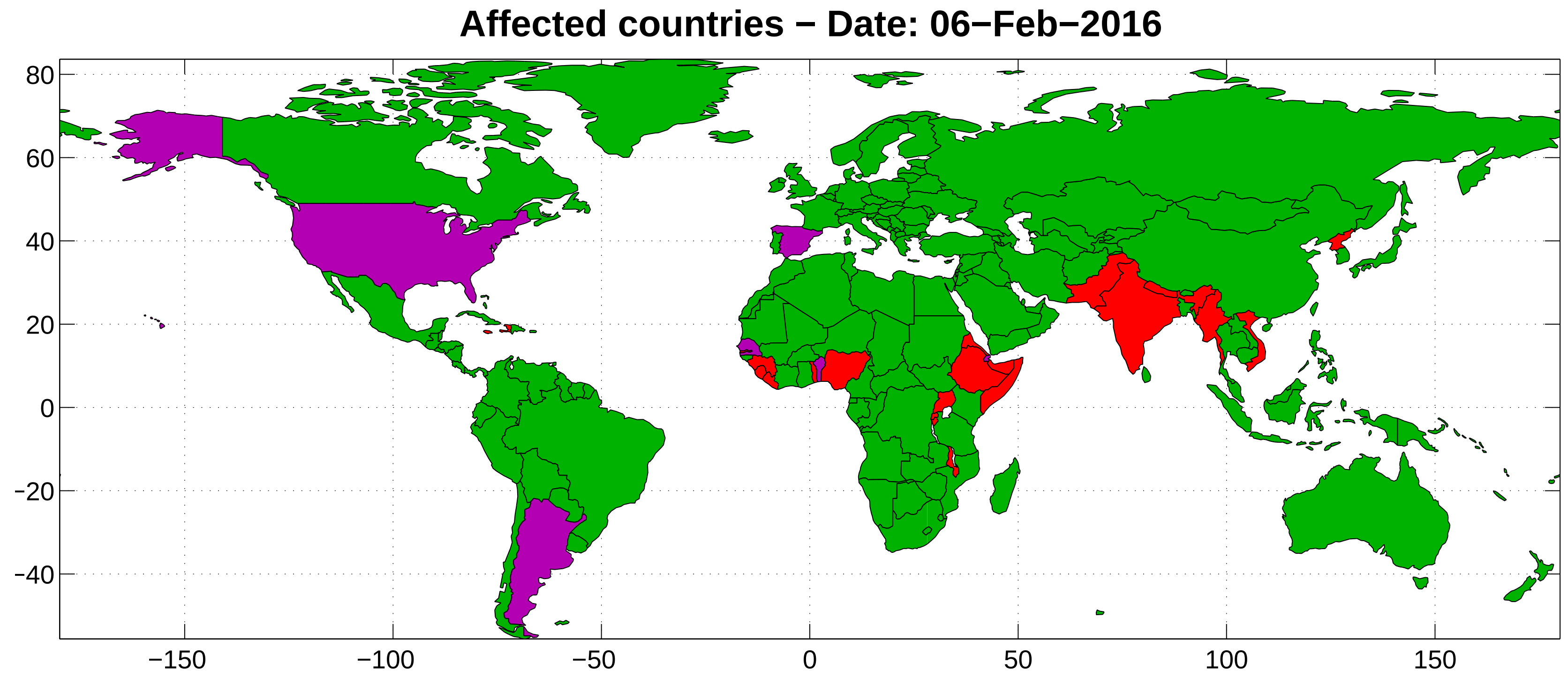
Application to EDV: Long term forecast



Application to EDV: Long term forecast



Application to EDV: Long term forecast



<10 cases: Benin, Senegal, Spain, United States of America, Djibouti, Argentina — ≥10 cases: Nigeria, Pakistan, Jamaica, Eritrea, Togo, Vietnam, India, Gambia, Ethiopia, Uganda, Nepal, Haiti, Malawi, Somalia, Somaliland, Burundi, Myanmar, Rwanda, North Korea, Guinea, Sierra Leone, Liberia.

Conclusions and perspectives

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Conclusions:

We have presented the Be-FAST and Be-CoDiS models for the study of some human and livestock diseases:

- Novel characteristics with respect to other models: Hybrid structure, dynamic coefficients, use of real databases.
- The results are consistent with real observations.
- Include the economical aspect (Be-FAST).

Next steps:

- Improve the calibration of the model (Be-CoDiS).
- Applications to risk management: Optimization of control measures.
- Extension to other diseases (African Swine Fever in Bulgaria/Sardinia).

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