EUFRAT web-based tool

Quantification of the risk of infection transmission by blood transfusion

Content

1. Introduction to modelling infection transmissions by blood transfusion

2. EUFRAT model for local outbreaks
   - Calculating number of infections transmitted
   - Distinguishing past and future transmissions

3. EUFRAT model for risks from travelling donors

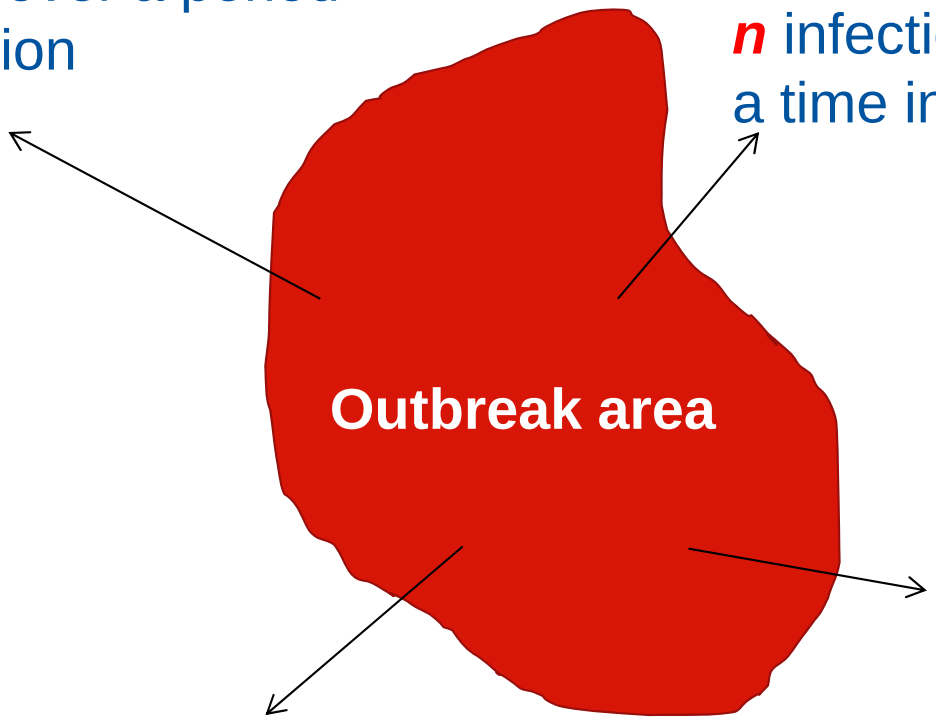
4. Dealing with parameter uncertainty

What you need to know to estimate the risk of infection transmission by blood transfusion

1) Number of infections
2) Duration of the outbreak
3) Number of exposed individuals
4) Number of exposed donors
5) Infectious period of the disease
6) Donation patterns
7) Likelihood of detection before blood transfusion
8) Products derived from one donation
9) Likelihood of transmission by blood transfusion

The EUFRAT model

The infectious disease is transmissible over a period D_a after infection

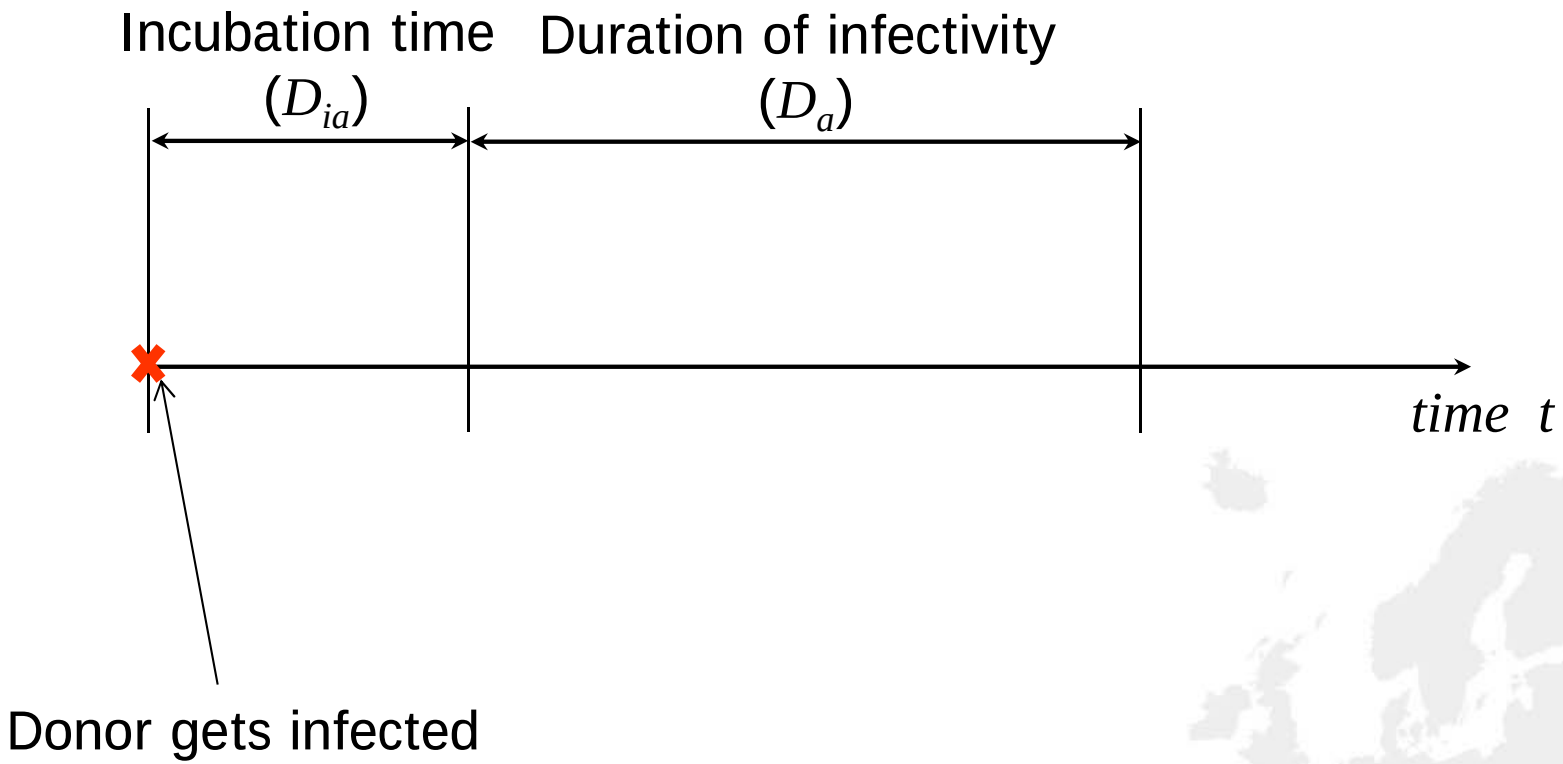


n infections observed in a time interval D_0

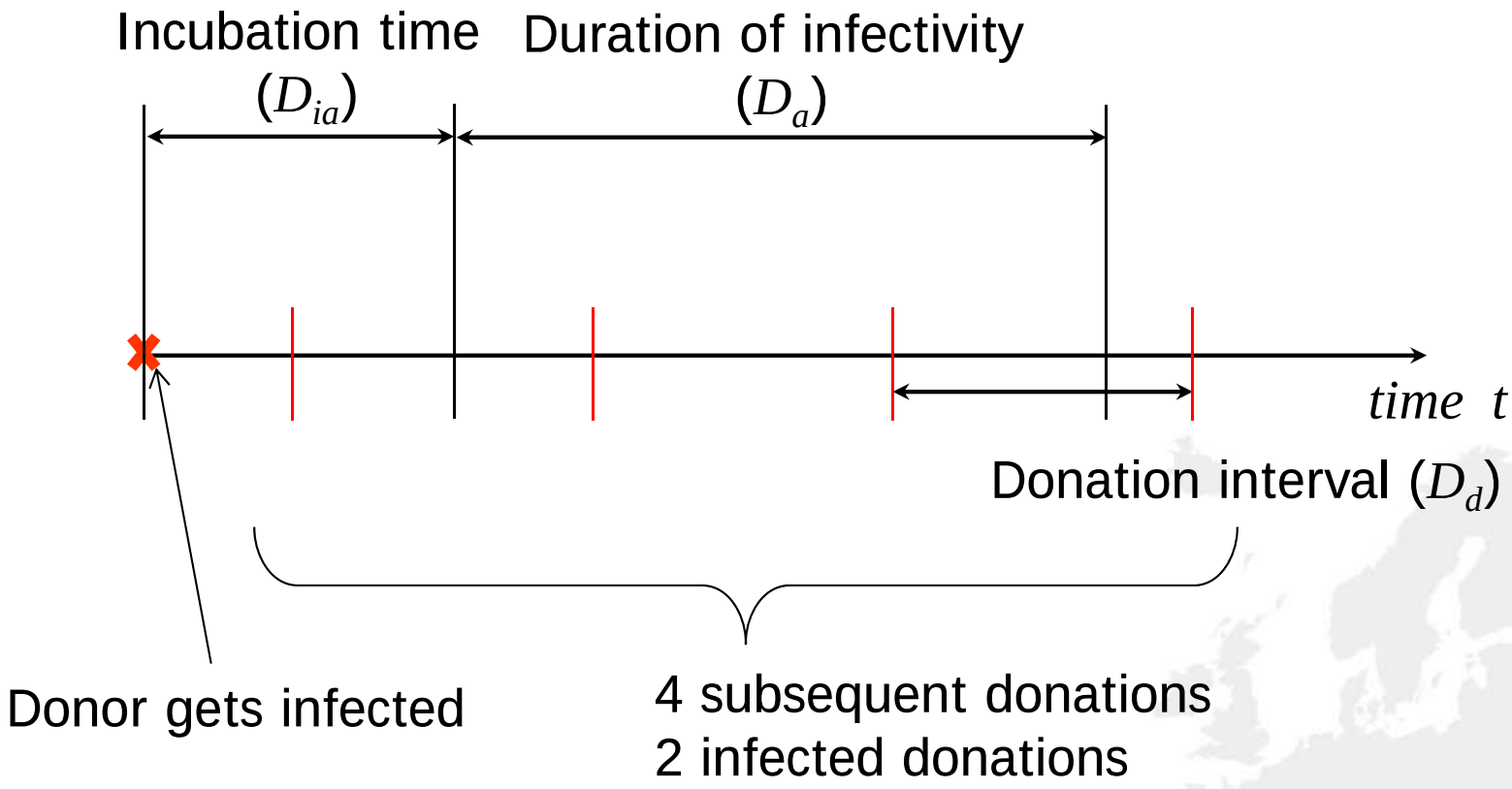
The outbreak area with ***N*** inhabitants, ***p%*** of which are blood donor

Donors on average donate after every D_d days

Introduction to modelling infection transmissions by blood transfusion



Introduction to modelling infection transmissions by blood transfusion



Number of infected donations is equal to:
Duration of infectivity / Donation interval

Example 1: Infections in donors

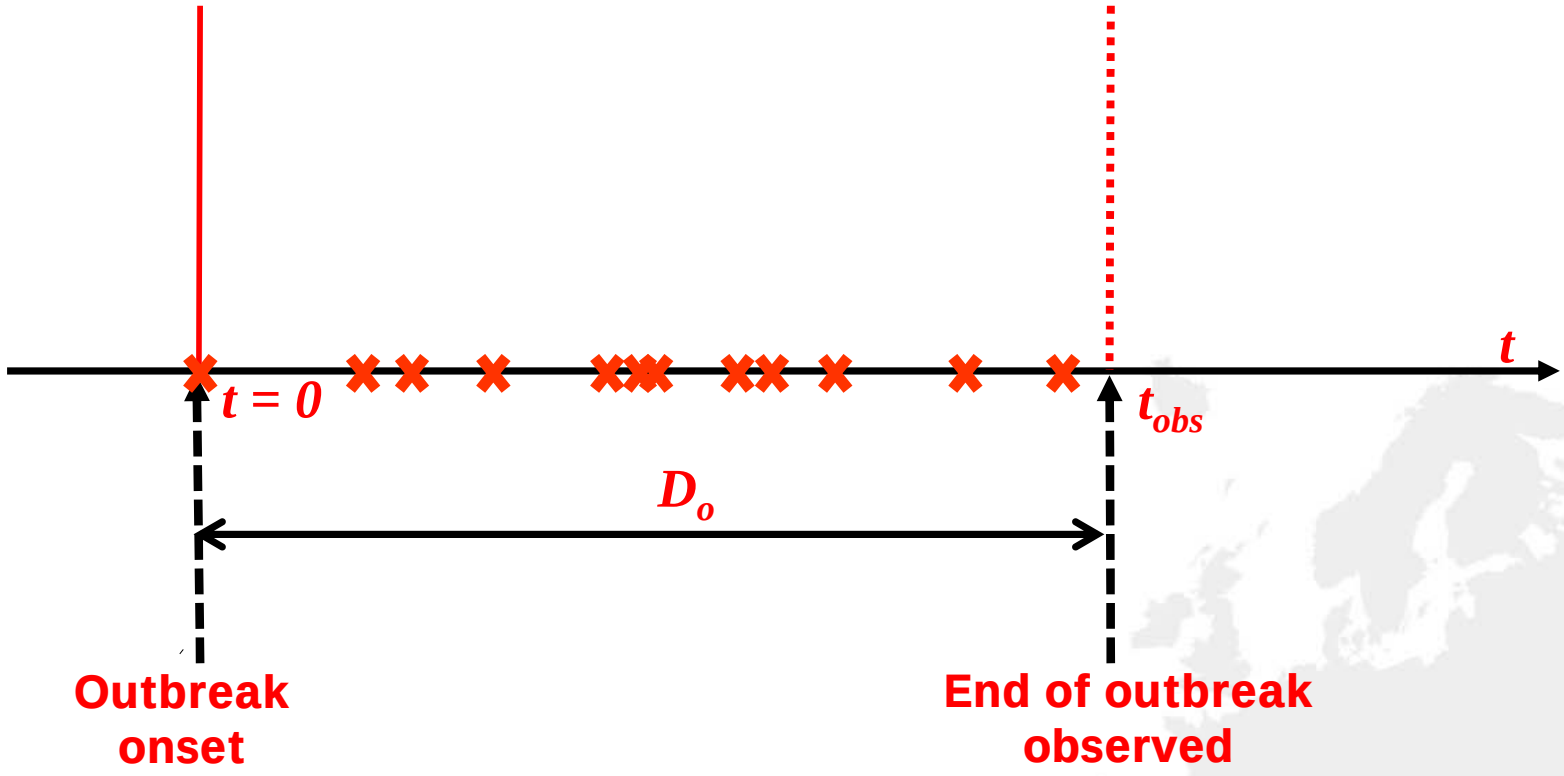
Description	Value
Population	100 000
Proportion donors	2%
Infections observed	20
Duration of the outbreak	1 month
Duration of infectivity	7 days
Donation frequency	2 times per year

How many infected donors would you expect?
20 * 2% = 0.40

How many infected donations will any infected donor make?
7/(365/2) = 1/26 = 0.038

How many infected donations will you expect in total?
0.40 * 0.038 = 0.015

Where does the epidemiology come in?



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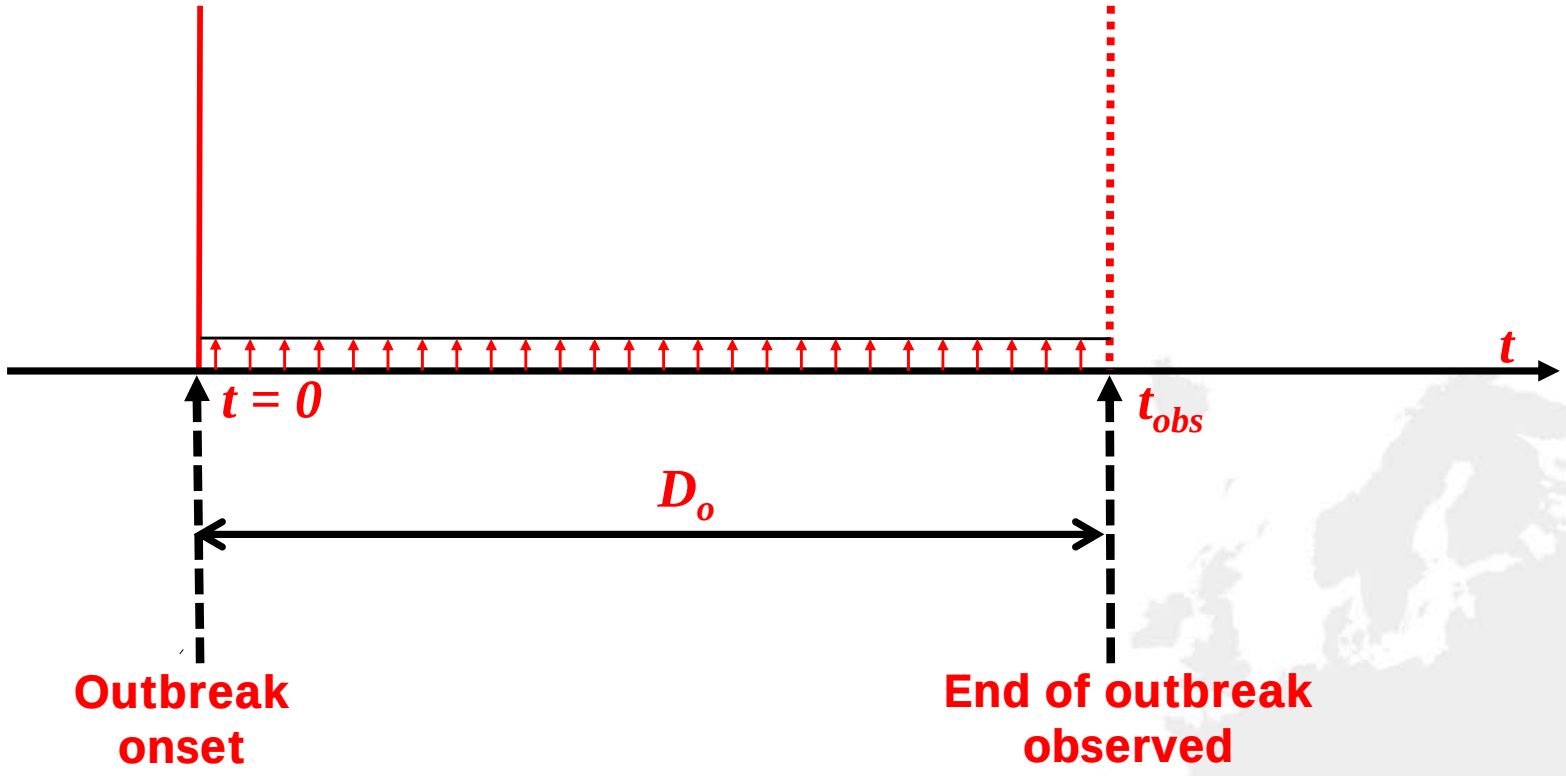

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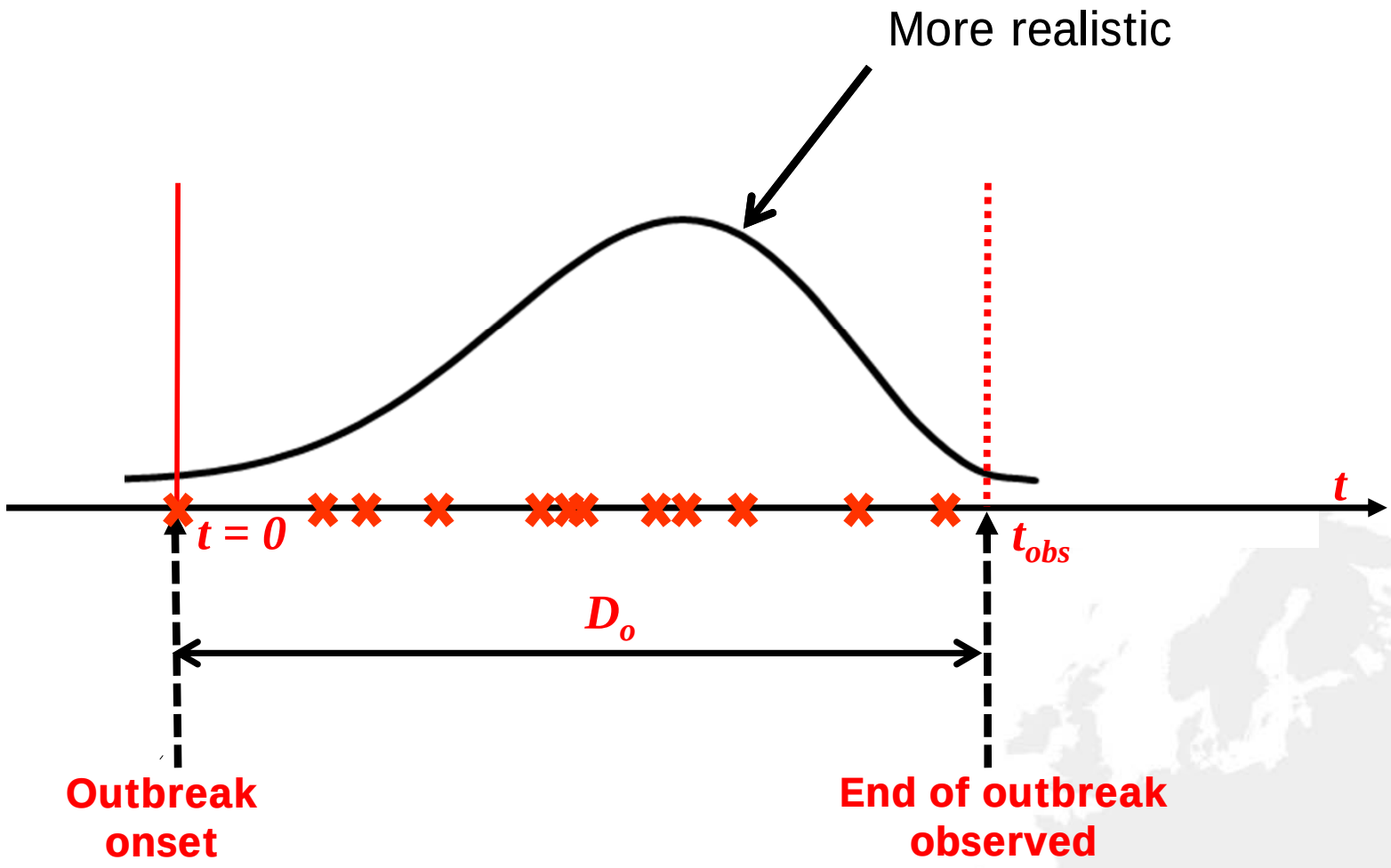

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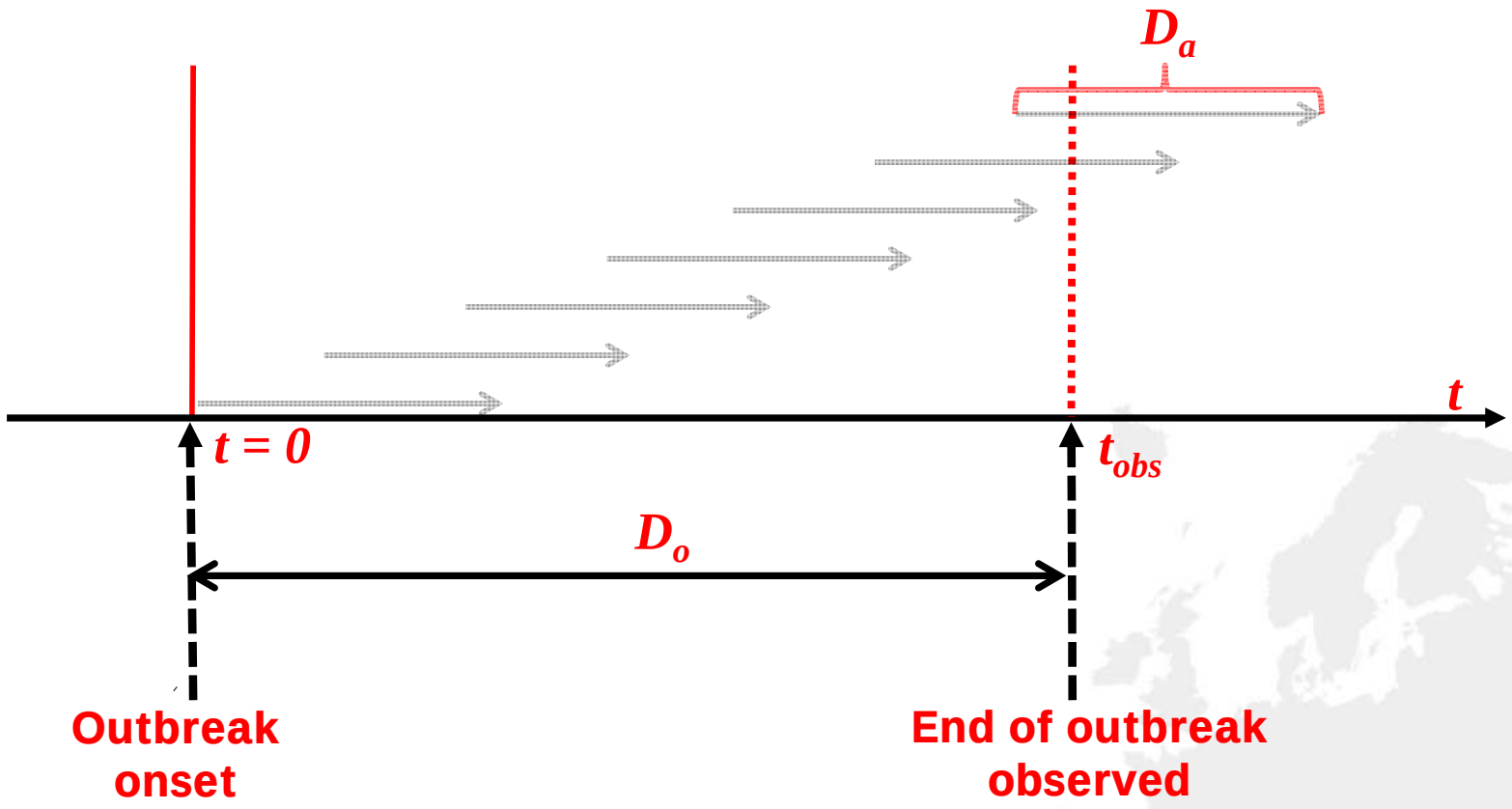
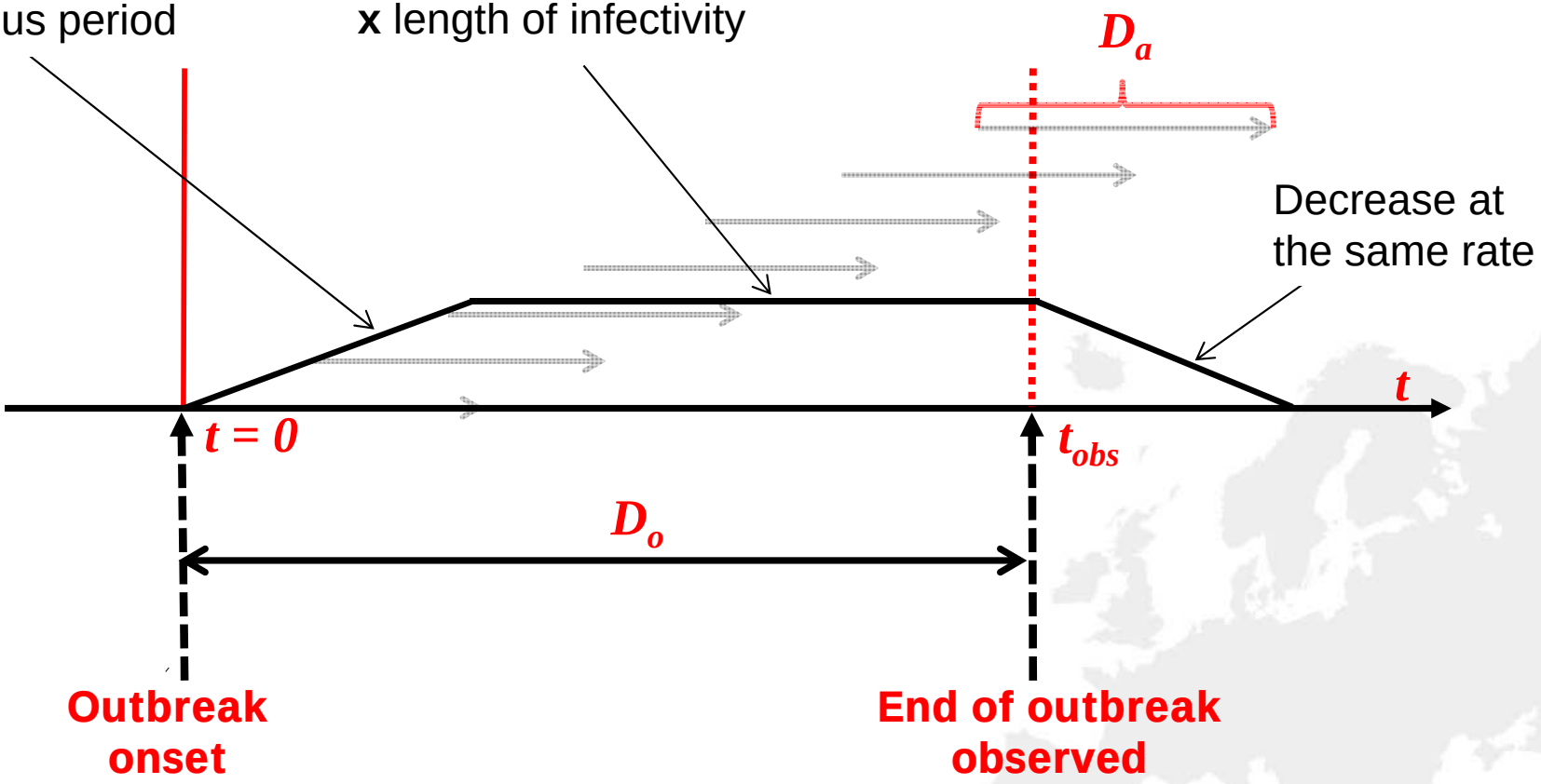


Prevalence of infection (infectious donors)

Increase over an interval as long as the length of infectious period

Stable prevalence, equal to:
Nr of Infections **/** Duration of outbreak
x length of infectivity



Example 1: prevalence among donors

Description	Value
Population	100 000
Proportion donors	2%
Infections observed	20
Duration of the outbreak	1 month
Duration of infectivity	7 days
Donation frequency	2 times per year

How many donors are infectious at the end of the outbreak?
= Infections per unit time x length of infectious period
= 20 / 4 * 1 = 5

Modelling Assumptions (1)

1. Donors have the same risk as any other individual	Correction for donor specific risk is implemented
2. No effect of infection on donation behaviour	If known this can be corrected for by adding a risk reduction factor
3. Infections evenly distributed over the interval considered	Note that this has **no impact** on total number of transmissions. If necessary the assessment can be split in subsequent time slots.
4. Duration of infectivity is known	Discuss later

From donations to products

Donors / Donations		Donation frequency	Contributions to final products* per year			
Donation types	**Donors**		**RBC**	**PLT**	**FPP**	**Total**
Whole blood (WB)	1000	2	2000	2000	2000	6000
Plasmapheresis (PP)	500	10			5000	5000
Total	**1500**	**5**	**2000**	**2000**	**7000**	**11000**

* Note that the column “Contributions to final products” refers to the **number of products obtained from individual donations**. For example distributed final PLT products may consist of PLTs obtained from five individual WB donations. The actual number of final products distributed from this example would in that case have been 400.

Example 1: Infected products

Description	Value
Population	100 000
Proportion donors	2%
Infections observed	20
Duration of the outbreak	1 month
Duration of infectivity	7 days

Donors		Donation frequency	Contribution to final products
WB	1000	2	6000
PP	500	10	5000
Total	**1500**	**5**	**11000**

How many infected products will you expect?

* For any infected WB donor this infection will result in:
  Probability of infected donation (2/52) * Nr of products (3) = 0.12
  Total number of infected products is: 0.12 * 0.40 * 2/3 = 0.031
* For any infected PP donor this infection will result in:
  Probability of infected donation (10/52) * Nr of products (1) = 0.19
  Total number of infected products is: 0.19 * 0.40 * 1/3 = 0.026

Example 1: Infected products

Description	Value
Population	100 000
Proportion donors	2%
Infections observed	20
Duration of the outbreak	1 month
Duration of infectivity	7 days

Donors		Donation frequency	Contribution to final products
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* For any infected PP donor this infection will result in:
  Probability of infected donation (10/52) * Nr of products (1) = 0.19
  Total number of infected products is: 0.19 * 0.40 * 1/3 = 0.026

Example 1: Infected products

Description	Value
Population	100 000
Proportion donors	2%
Infections observed	20
Duration of the outbreak	1 month
Duration of infectivity	7 days

Donors		Donation frequency	Contribution to final products
WB	1000	2	6000
PP	500	10	5000
Total	**1500**	**5**	**11000**

How many infected products will you expect?
This is identical to:

Number of infected donors (20 * 2%)
x Proportion of time infective (1/52)
x Exposure of recipient population (11000/1500)

= 0.40 * 0.019 * 7.3 = 0.056 (0.14 transmissions per infection)

Example 1: Infected products

Description	Value
Population	100 000
Proportion donors	2%
Infections observed	20
Duration of the outbreak	1 month
Duration of infectivity	7 days

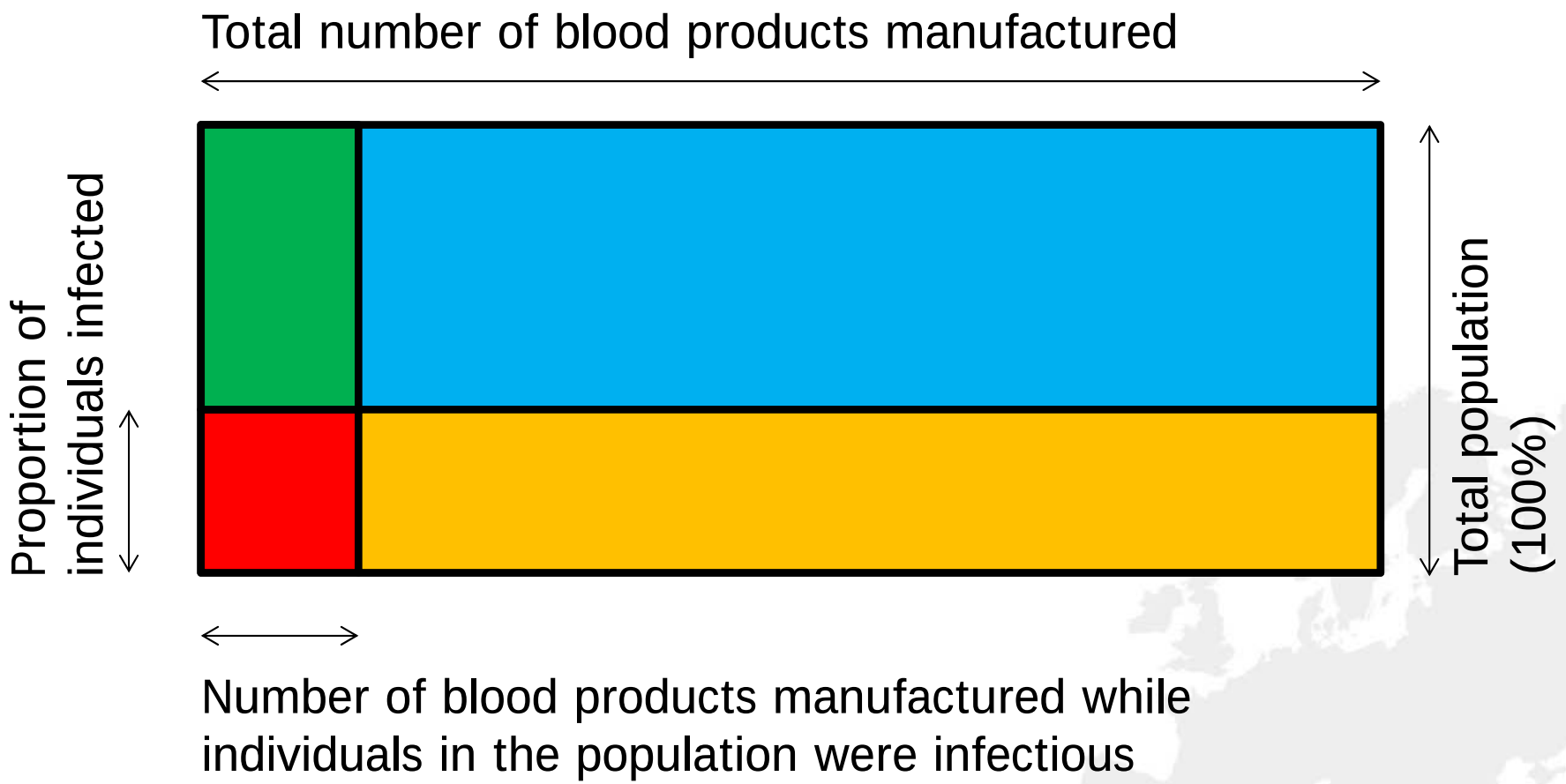
Donors		Donation frequency	Contribution to final products
WB	1000	2	6000
PP	500	10	5000
Total	**1500**	**5**	**11000**

How many infected products will you expect?
This is identical to:

Proportion of the population infected (20 / 100 000)
* Products exposed to infectivity (11 000 x 1 / 52)

= 11 000/100 000 * 20 / 52 = 0.056

Proportion of the population affected, number of products manufactured and duration of infection determine everything



What you need to know to estimate the risk of infection transmission by blood transfusion

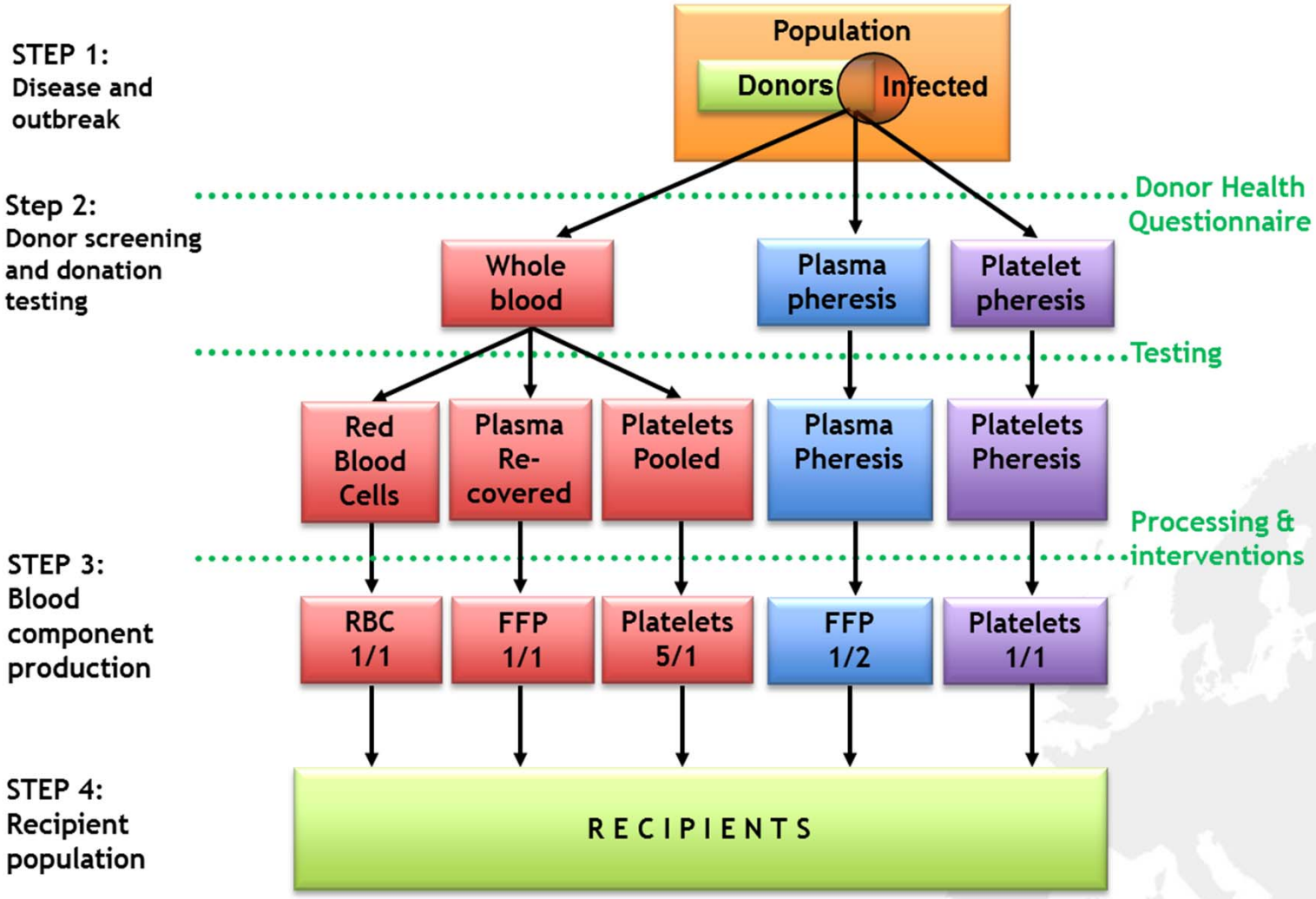
1) Number of infections
2) ~~Duration of the outbreak~~
3) Number of exposed individuals
4) ~~Number of exposed donors~~
5) Infectious period of the disease
6) ~~Donation patterns~~
7) Likelihood of detection before blood transfusion
8) Products derived ~~from one donation~~
9) Likelihood of transmission by blood transfusion

Modelling Assumptions (2)

1. All donors have the same risk	No differentiation is made between various donor subpopulations This can be assessed by considering populations individually
2. The ***average risk of transmission***, so the <u>expected average number of infected recipients</u>, is calculated by *EUFRAT*	

EUFRAT steps

Tool steps:



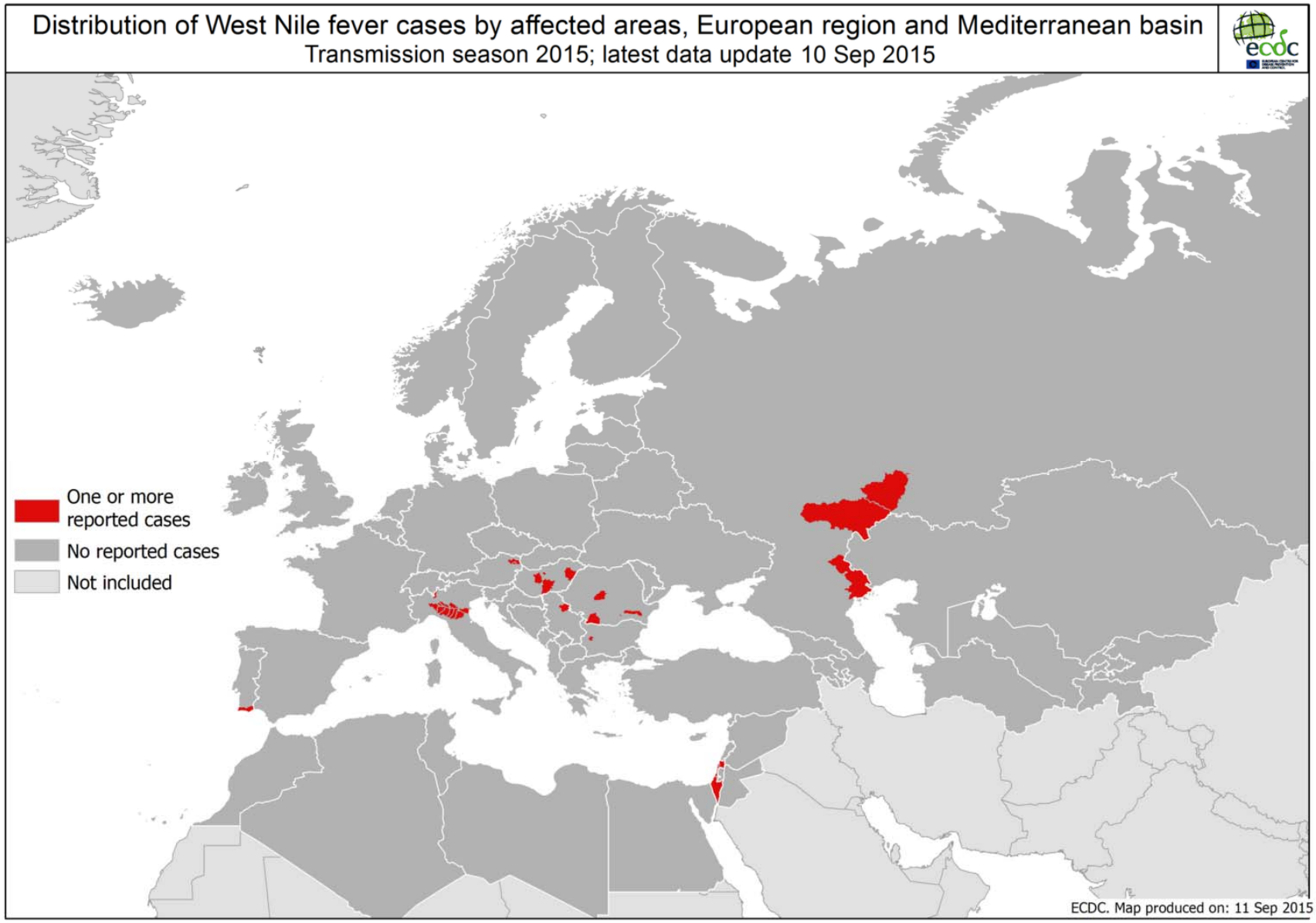
Safety Interventions / Risk reduction

Intervention	Model parameters
Donor health questionnaire	• Presence of detectable disease characteristics • Effectiveness of identification by questionnaire
Donation testing	• Test coverage • test sensitivity
Separation and/or treatment of components	• Risk reduction factor per product type

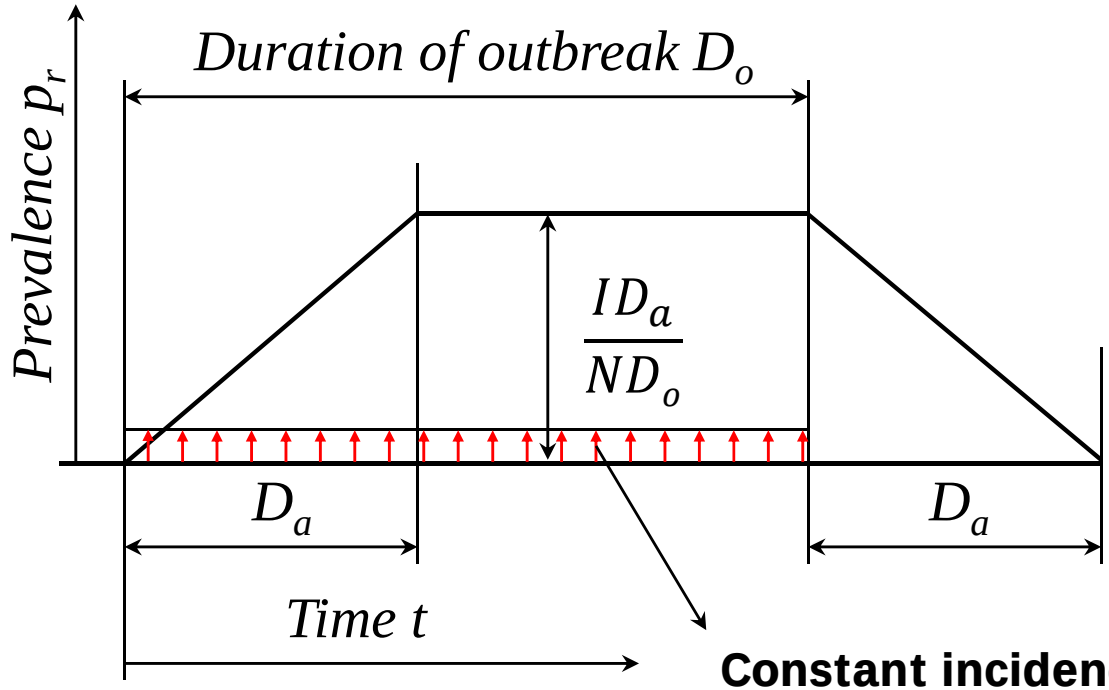
Recipient population characteristics

Description	Model parameters
A transmission may lead to different categories of disease expression (e.g. flu like symptoms, encephalitis, death)	• Proportion of characteristic disease outcomes per infectious case
Recipient susceptibility may differ: there may be immunity for the disease among patient groups	• Specific immunity in the recipient population per product type (the proportion of recipients that are immune against the pathogen)

Back to the epidemiology



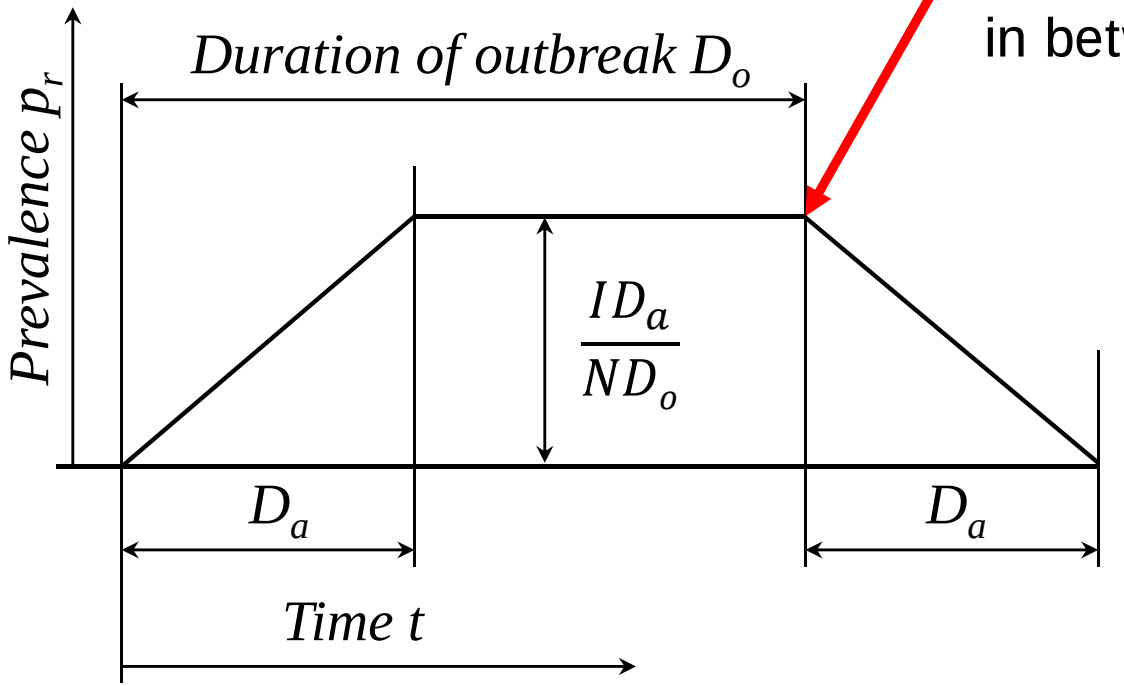
Incidence and Prevalence of infection as a function of time since infection



Constant incidence rate:

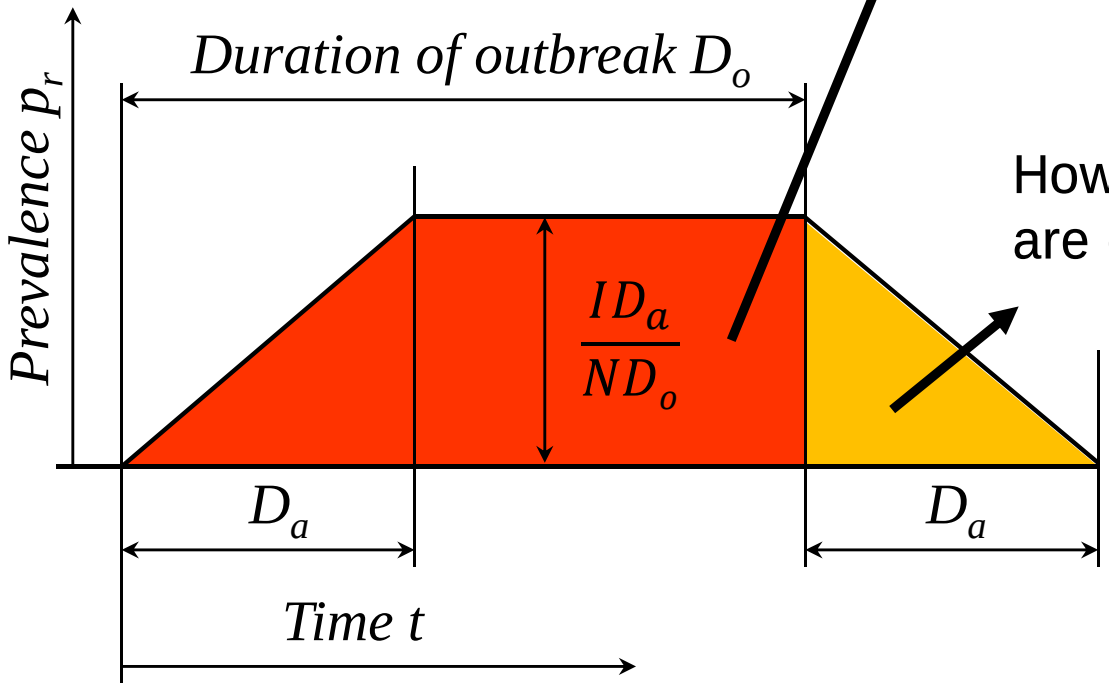
I/ND_o

Incidence and Prevalence of infection as a function of time since infection



A mixture of individuals at the beginning and at the end of their infectious period (and everything in between)

Time of transfusion transmission



How many transmissions have occurred already?

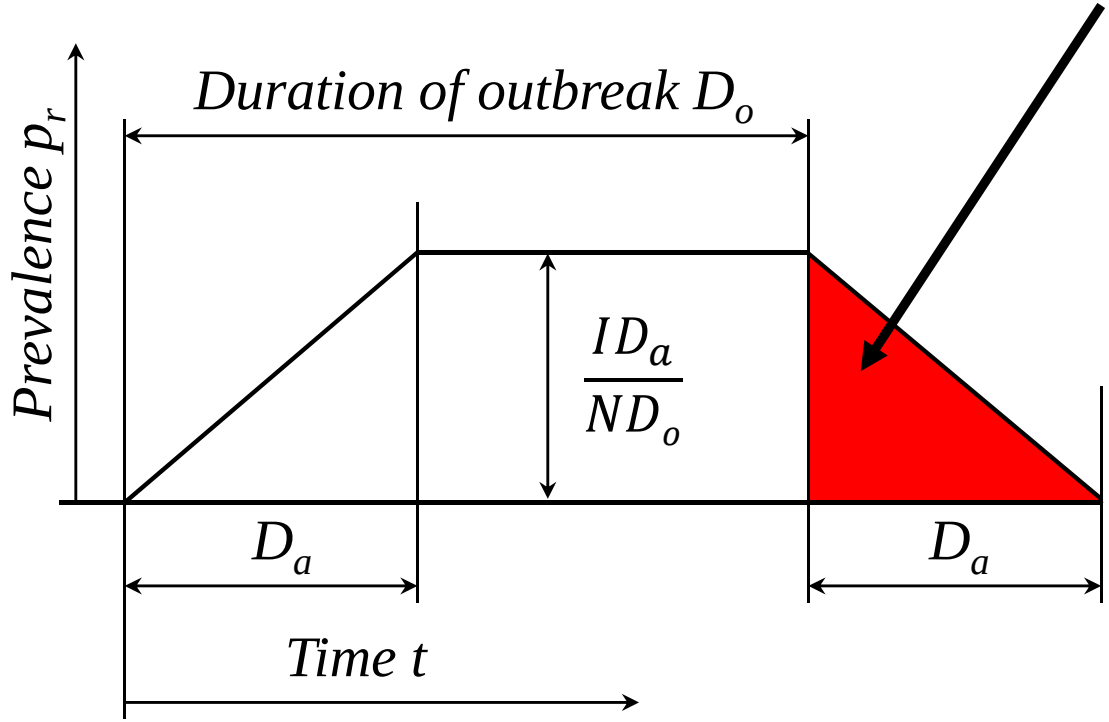
Guide communication with recipients

How many transmissions are expected yet to occur?

Guide requirements for interventions to prevent future transmissions by exposed donors

Time of transfusion transmission: transmissions after the outbreak when $D_0 \geq D_a$

Future infections:
Total infections * ½ D_a/D_0



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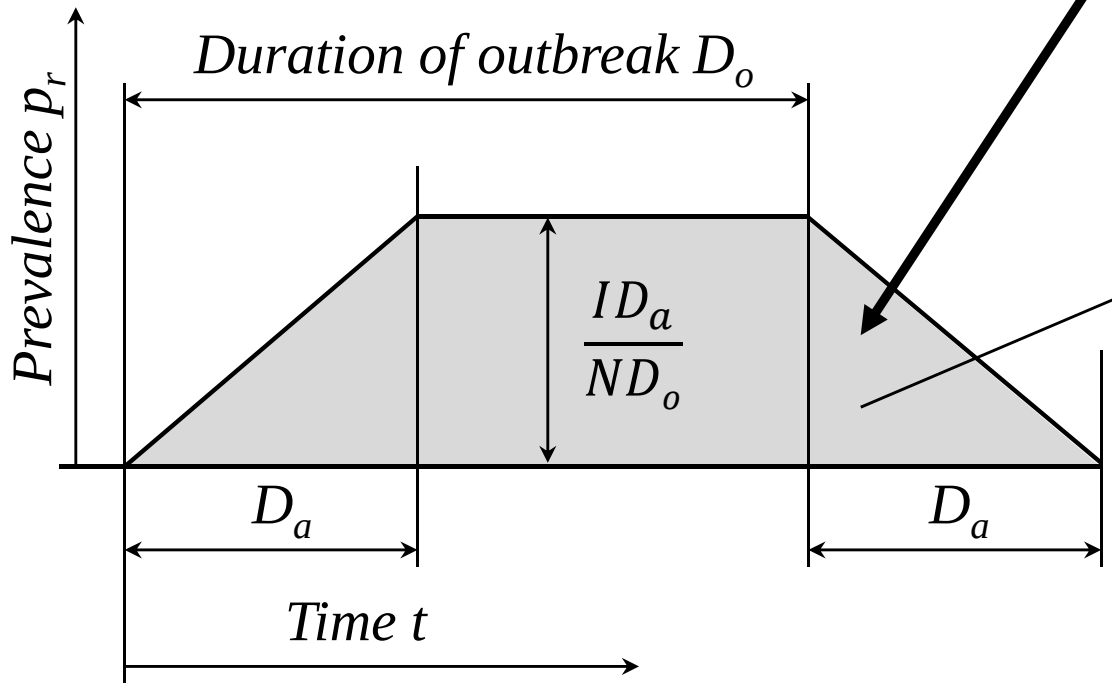
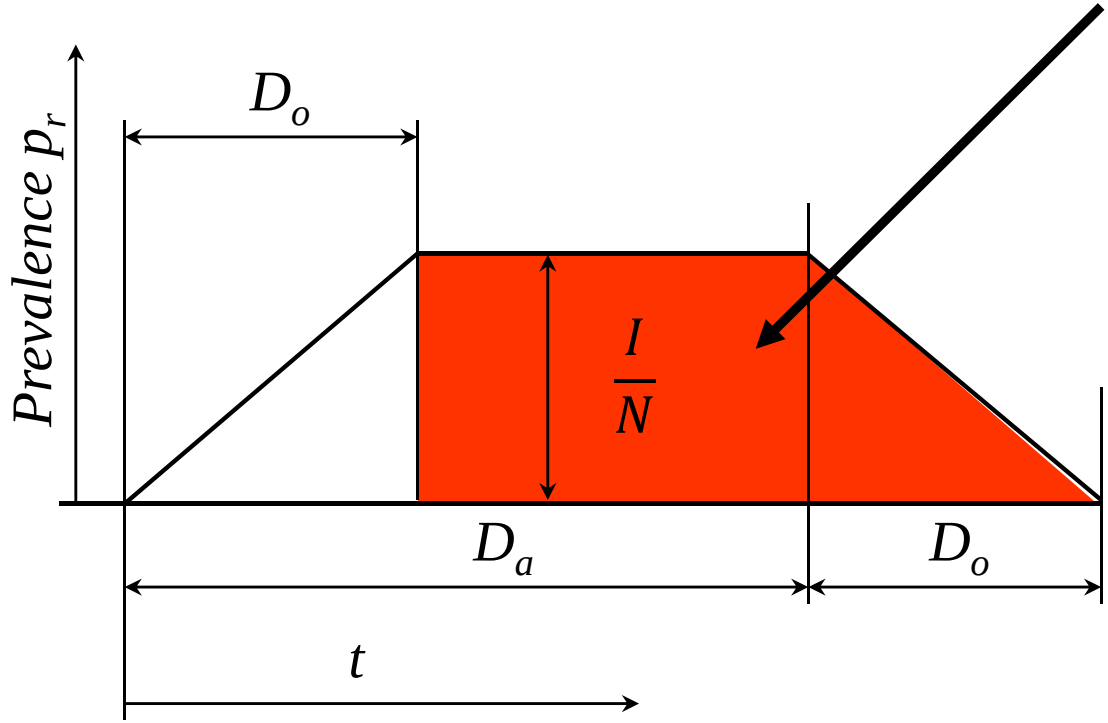


Total Area: $O = \frac{ID_a}{N}$

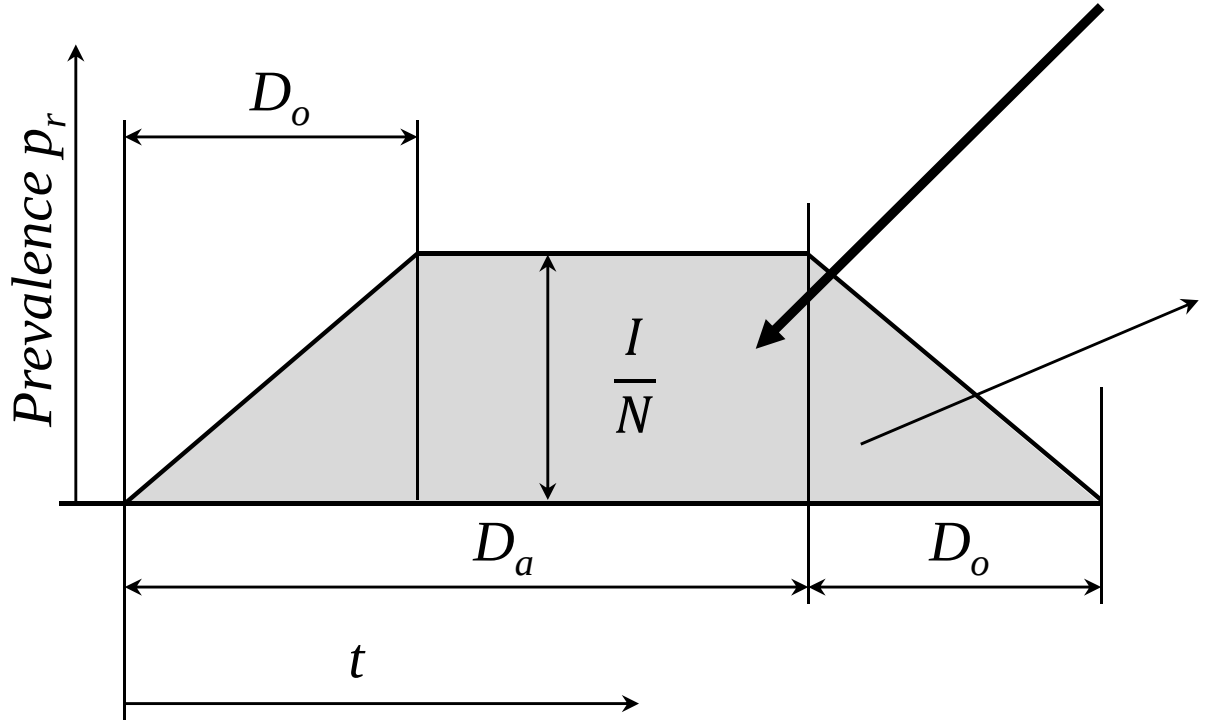
Time of transfusion transmission: transmissions after the outbreak when $D_0 \leq D_a$

Future infections:
Total infections * (1-½ D_0/D_a)



Time of transfusion transmission: transmissions after the outbreak when $D_0 \leq D_a$

Future infections:
Total infections * (1-½ D_0/D_a)



Total Area: $O = \frac{ID_a}{N}$

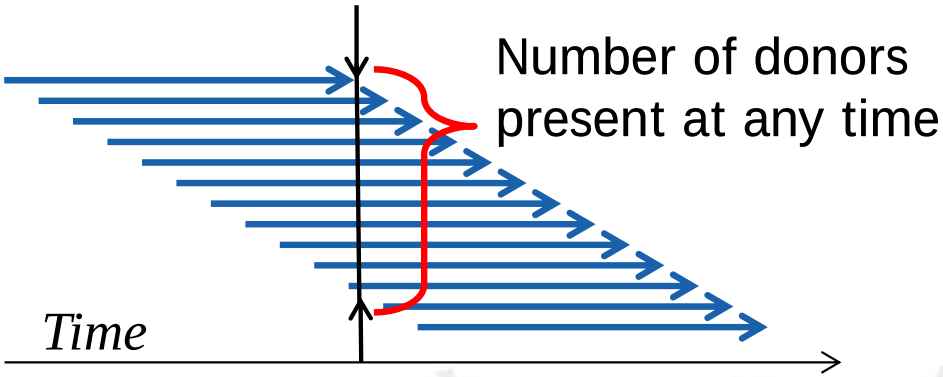
The duration of the infectious period determines the number of transmissions, the duration of the outbreak determines the timing of these transmissions

Risks from Travelling donors

Differences from an endemic exposure

1) Limited exposure
   - Defined by donors per day and duration of travel

Number of donors at any time is equal to the **number of donors arriving per unit time x duration of stay**



2) Restrictions from donating
   - Donors can only donate upon return upon home

Risks from Travelling donors

Infection free area

Infection risk area

Traveling donors:
1. Rate of travel

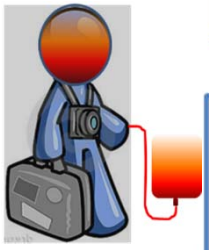
Visiting

Exposure:
1. Time and length of stay of traveling donors
2. Incidence of infection among local population

Returning

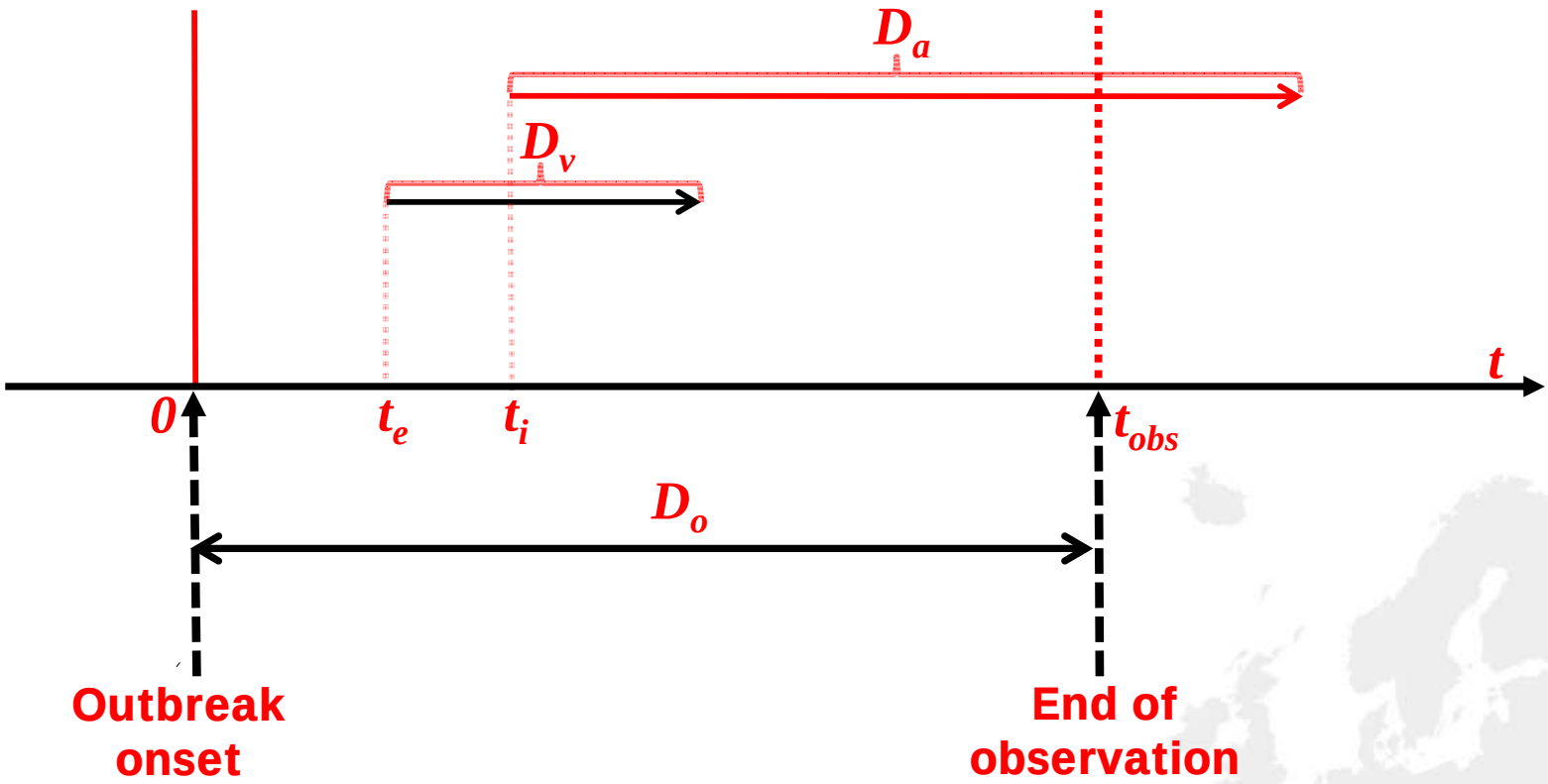
Returning donors:
1. Risk of being infected

Infected donors:
1. Risk of getting infected



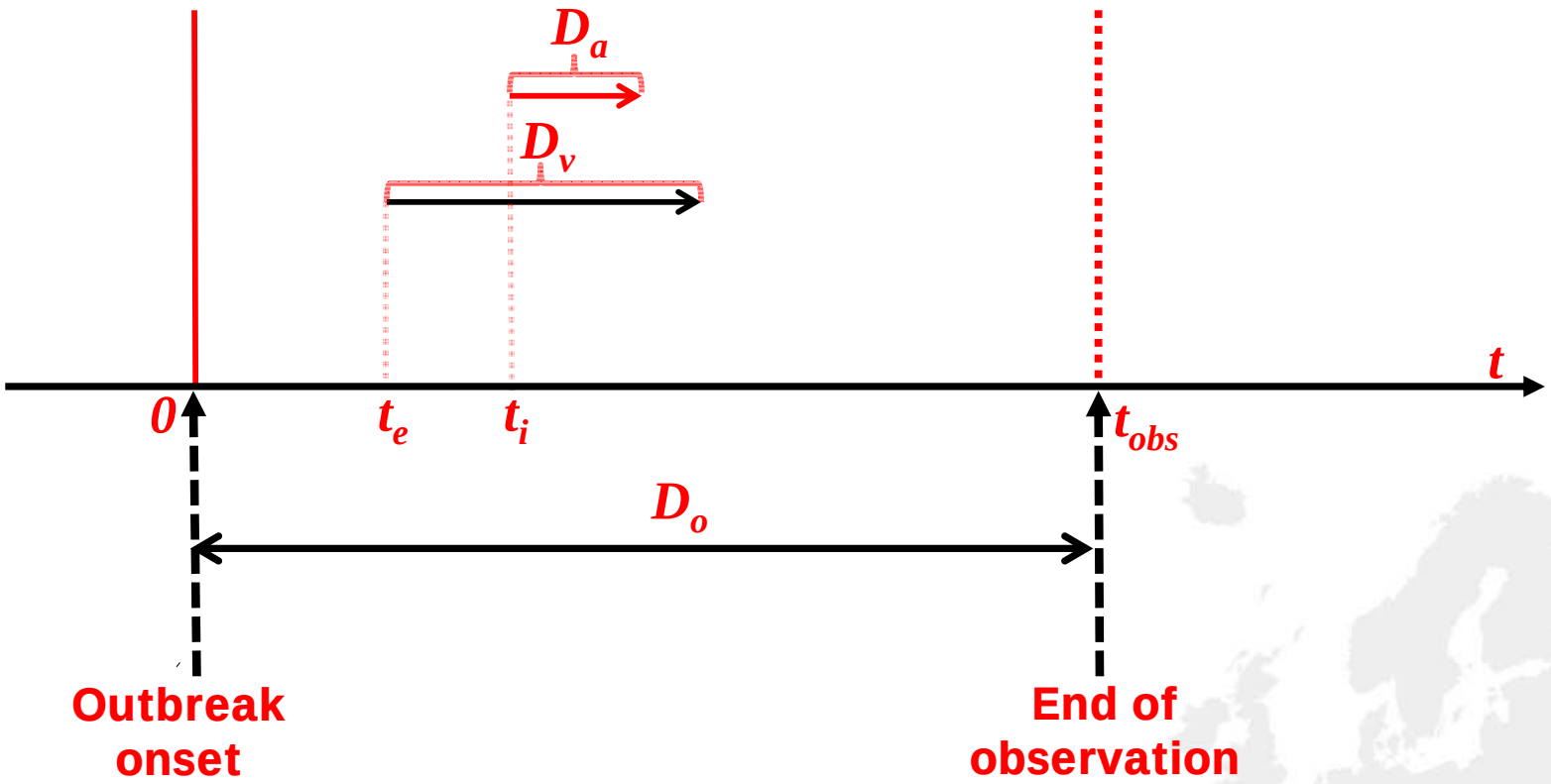
Infected donations and recipients:
1. Donation frequency
2. Length of infectivity
3. Safety measures in transfusion practice
4. Blood components preparation
5. Transfusion transmission probability

Travelling donor transmissions



The time for potential transmission during the infectious period will now on average be (D_a-D_v/2) instead of D_a

Travelling donor transmissions



The time for potential transmission during the infectious period will now on average be (D_a-D_a/2)= D_a/2 instead of D_a

Modelling Assumptions (3)

1. No impact of travel on donation behaviour	Such an effect is very likely but requires further study before it can be incorporated into the risk models
2. Travel characteristics are known	Average estimates are obtainable and should suffice
3. Travelling donors are presumed to have the same exposure as the resident population	Outbreaks might be very local and travellers exposure therefore over- or under-estimated
4. Repeated infections are ignored	Might occur on extended stays. Early infections will reduce the risk of transmission

Just some slight extensions

1. *EUFRAT* allows to incorporate a “proportion of undetected cases”. This corrects for underestimating the actual number of infections when entering the number of observed infections during an outbreak.

2. *EUFRAT* allows correction for the risk of infection of donors as compared to the general population

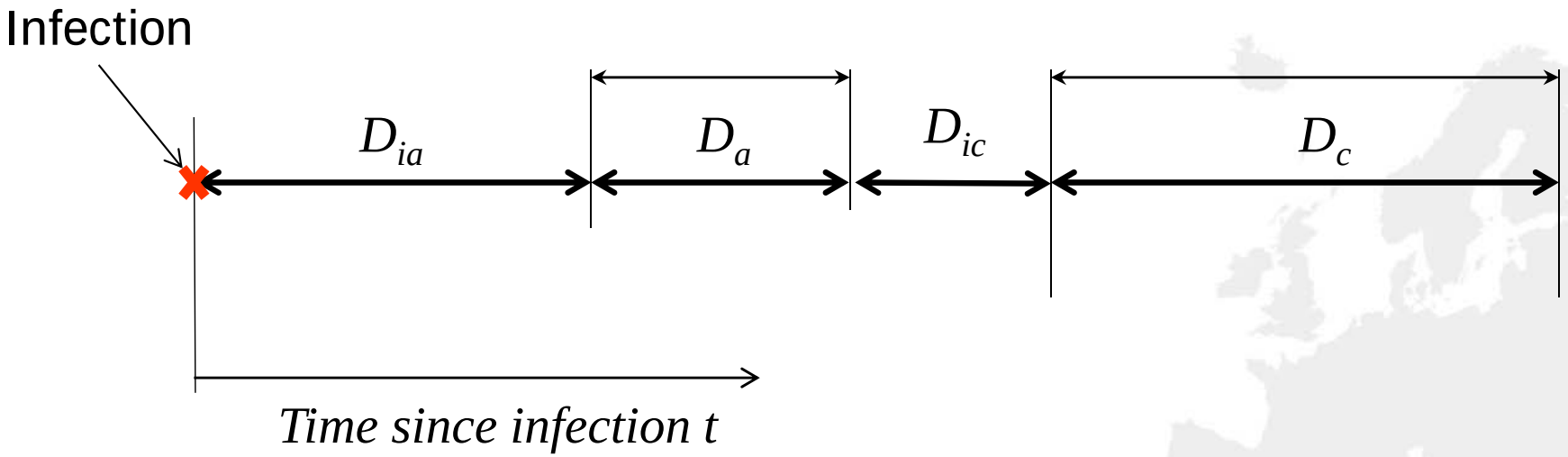
3. At the end of the acute infection, there might be a proportion of infected donors that develop a chronic infection, with an associated infectious period.

4. Both the acute and chronic infectious periods may be delayed for a given period of time.

Donor infectivity over time

Infectious period of acute infection, where transmission is possible

Infectious period of chronic infection, where transmission is possible



Model validation Dengue in Surinam and the Dutch Caribbean

I – EUFRAT risk estimate

1) infections in outbreak region
2) travellers exposure (number of travellers per year, duration of visit)
3) proportion of donors among travellers
4) calculate number of expected infected donors

II – Validation estimate

1) Dengue infections identified in Dutch laboratories
2) travel history to Surinam or Dutch Caribbean
3) proportion of donors among travellers
4) calculate number of expected infected donors

III – Compare estimates

Model validation Dengue in Surinam and the Dutch Caribbean

Description	Suriname (95%CI)	Dutch Caribbean (95%CI)
Cumulative number of infected travelling donors in 2001-2011 estimated by EUFRAT model	5.2 (2.4-11)	86 (45-179)

Model validation Dengue in Surinam and the Dutch Caribbean

Description[1]	Suriname (95%CI)	Dutch Caribbean (95%CI)
Cumulative number of infected travelling donors in 2001-2011 estimated by EUFRAT model	5.2 (2.4-11)	86 (45-179)
Cumulative number of infected travelling donors in 2001-2011 inferred from infections in the general Dutch population (lab-based study) [2]	18 (9.3-60)	28 (14-92)
Ratio EUFRAT: lab-based study estimates[2]	0.30	3.3

[1]Oei *et al.* Estimating the risk of dengue transmission from Dutch blood donors travelling to Suriname and the Dutch Caribbean. Vox Sanquinis, accepted for publication

[2]Cleton *et al*. Using routine diagnostic data as a method of surveillance of arboviral infection in travellers. Travel.Med.Infect.Dis. 2014.

This presentation should have allowed you to understand

1. All relevant model parameters used in the *EUFRAT* tool
2. How *EUFRAT* estimates the number of infections in donors
3. How *EUFRAT* calculates the transmission of infections to transfusion recipients
4. The difference between past and future infection transmissions as applied in *EUFRAT*
5. Know how *EUFRAT* calculates the risk from travelling donors

Questions?