

# Outbreak response analytics

When are pathogen genomes useful?

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SMBE Satellite Workshop

London School of Hygiene and Tropical Medicine  
Imperial College London

# Emerging disease, early outbreak response context



- situational awareness urgently needed
- limited data available
- questions focus on delays, risk factors, transmissibility
- reproducibility and reliability » refinement and complexity

# Emerging disease, early outbreak response context



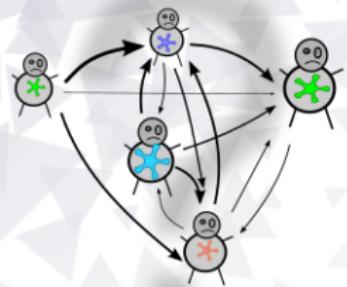
- situational awareness urgently needed
- limited data available
- questions focus on delays, risk factors, transmissibility
- reproducibility and reliability » refinement and complexity

How can data analytics / modelling help?

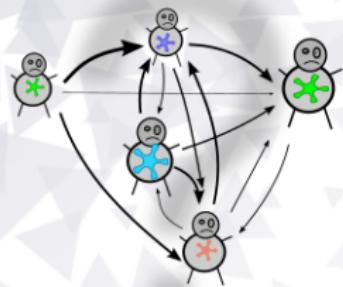
# Reconstructing transmission trees

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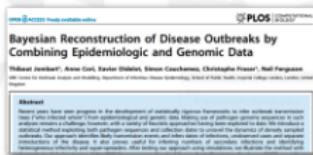
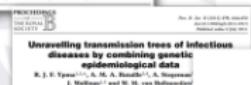
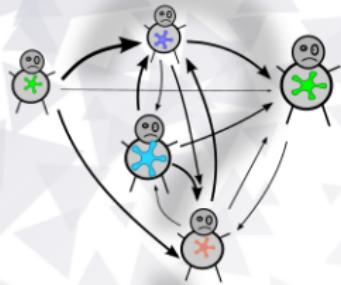
# Using genomics to infer who infects whom?



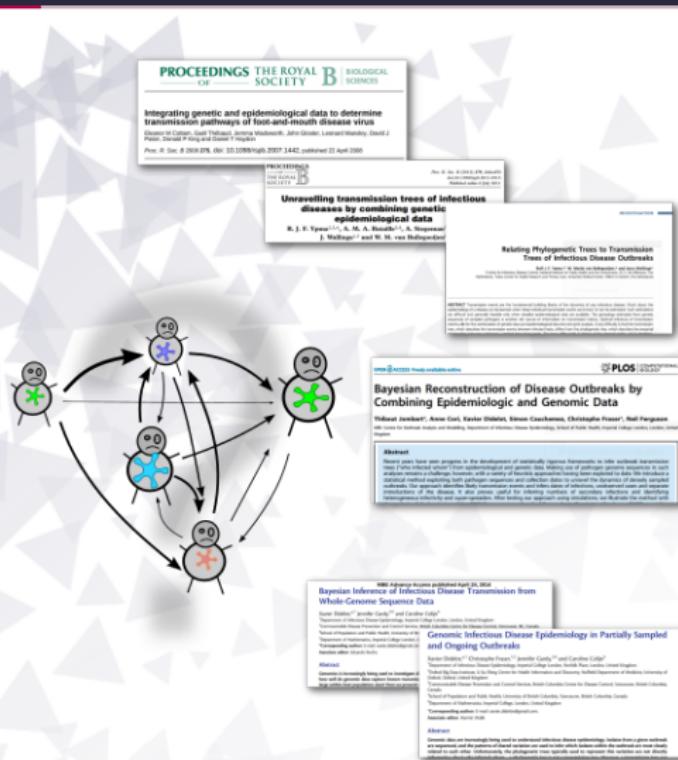
## Using genomics to infer who infects whom?



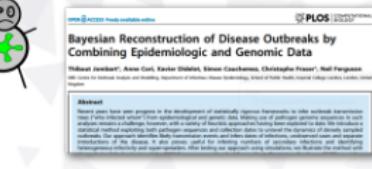
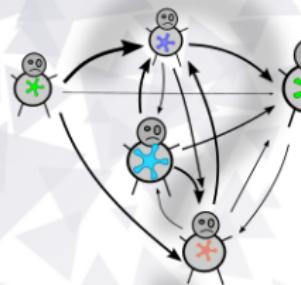
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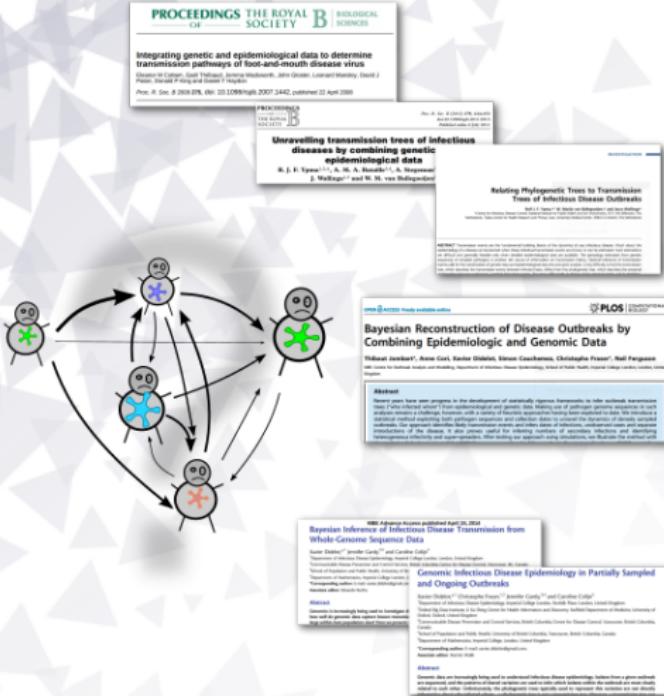
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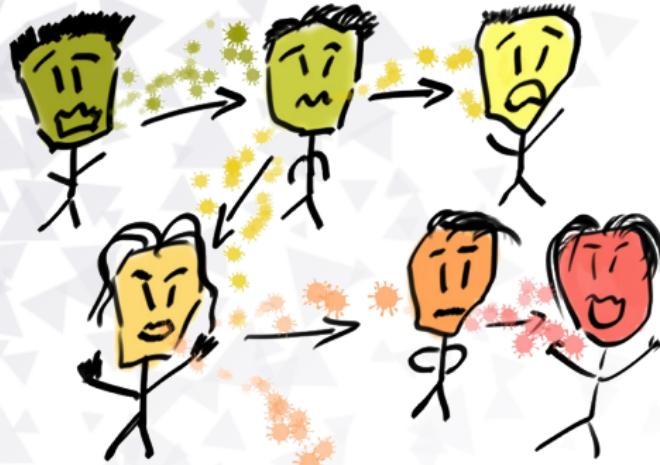


# Using genomics to infer who infects whom?



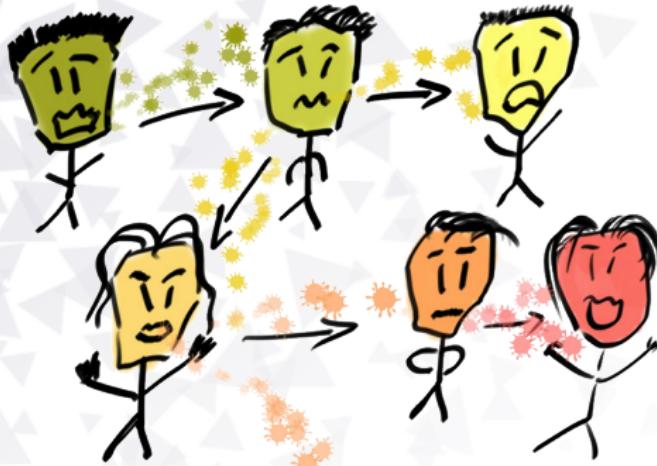
Methods heavily  
rely on whole genome  
sequence data

# Using WGS to infer who infected whom



Mutations accumulate along transmission chains.

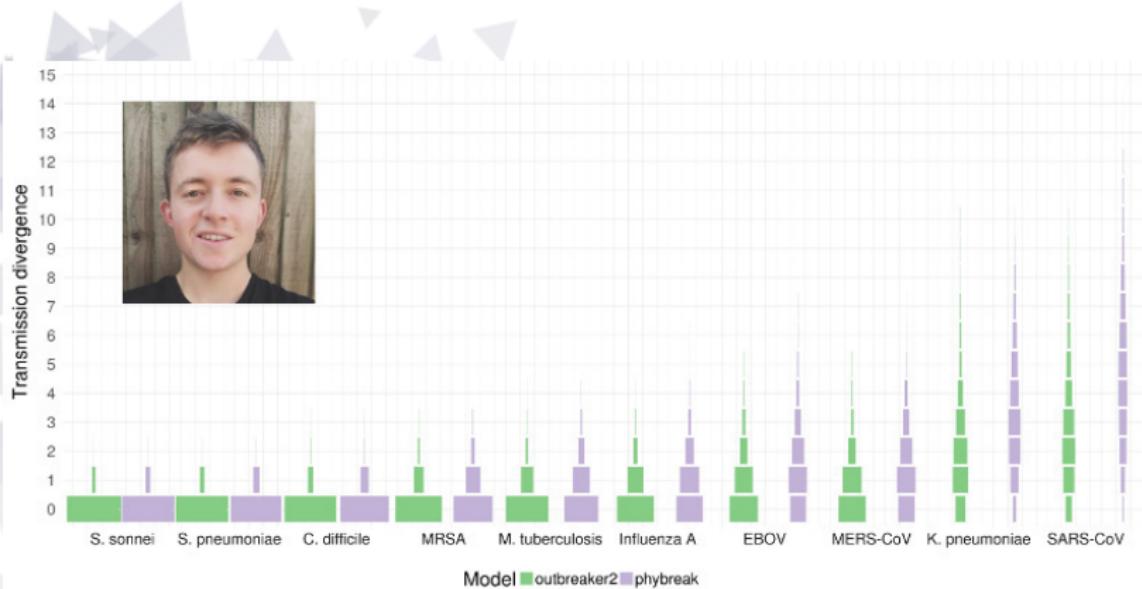
# Using WGS to infer who infected whom



Mutations accumulate along transmission chains.

Can be used to reconstruct transmission trees.

# How informative are whole genome sequences?



[Campbell et al. (2018) PLoS Pathogens]

Insufficient diversity for most diseases.

# Evidence synthesis approach to outbreak reconstruction



Combine different data to shrink the set of plausible trees.

# *outbreaker2*: evidence synthesis framework for outbreak reconstruction

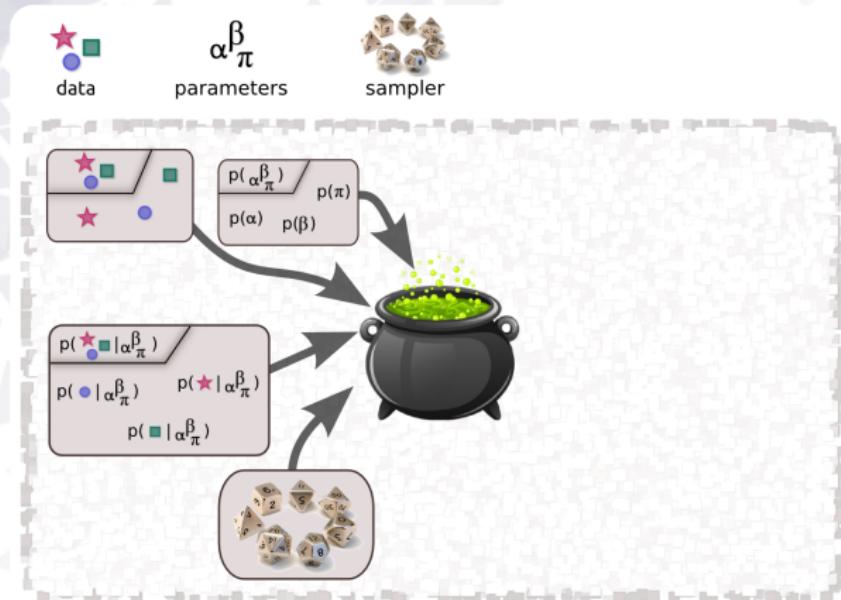
**Modularity:** customise data, prior, likelihood, MCMC.



[Campbell *et al.* (2018) BMC Bioinformatics]

# *outbreaker2*: evidence synthesis framework for outbreak reconstruction

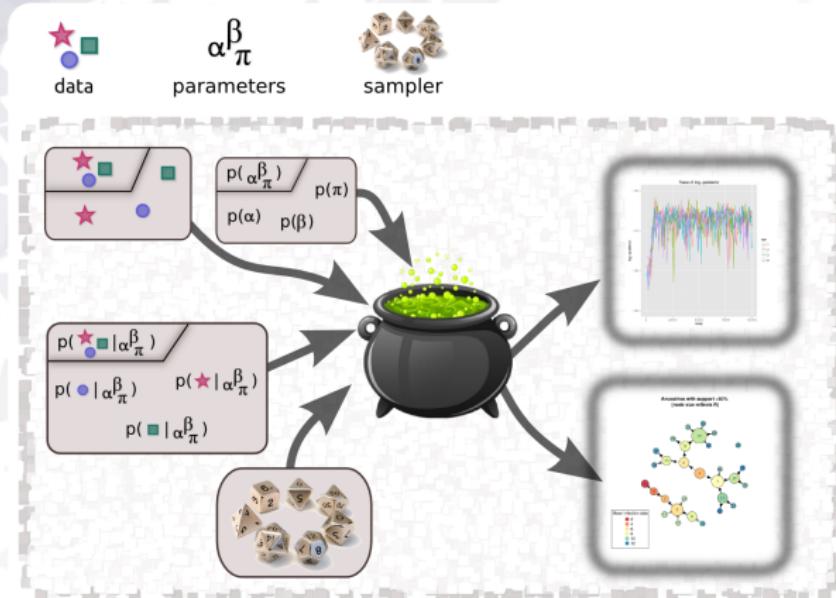
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[Campbell *et al.* (2018) BMC Bioinformatics]

# *outbreaker2*: evidence synthesis framework for outbreak reconstruction

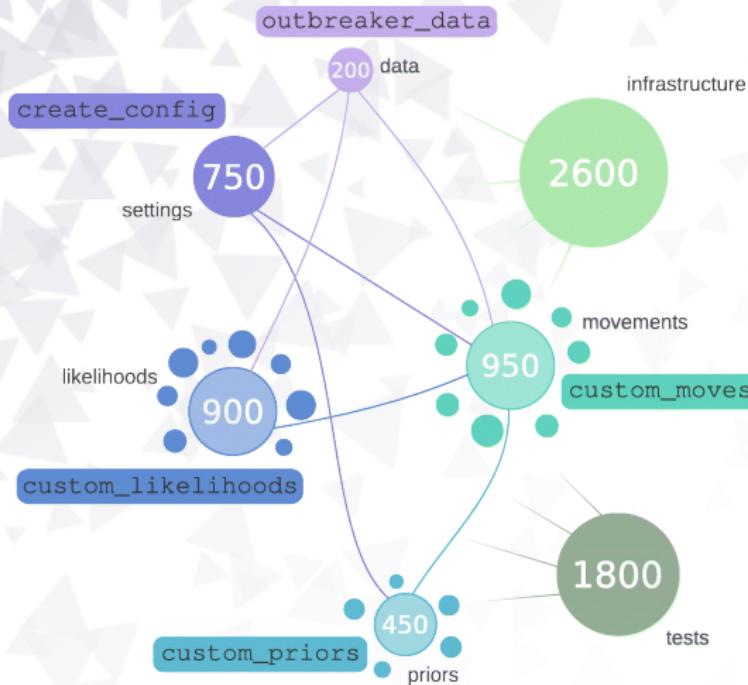
**Modularity:** customise data, prior, likelihood, MCMC.



[Campbell *et al.* (2018) BMC Bioinformatics]

# What is inside the pot?

Module sizes in lines of code, and entry points:



## Example: implementing *TransPhylo* in *outbreaker2*

### *outbreaker* likelihood

- $p(s, t | \alpha, T^{inf}, \kappa, \mu, \pi) = p(T^{inf} | \alpha, \kappa) p(T^{inf} | t) p(s | \alpha, \kappa, \mu) p(\kappa | \pi)$
- i.e. *timing infection*  $\times$  *incubation*  $\times$  *genetic (simple)*  $\times$  *missing cases*

## Example: implementing *TransPhylo* in *outbreaker2*

### *outbreaker* likelihood

- $p(s, t | \alpha, T^{inf}, \kappa, \mu, \pi) = p(T^{inf} | \alpha, \kappa) p(T^{inf} | t) p(s | \alpha, \kappa, \mu) p(\kappa | \pi)$
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### *TransPhylo* likelihood

- $p(G | \beta, \gamma, N_{eg}, \alpha) = p(G | N_{eg}, \alpha) \times p(\alpha | \beta, \gamma)$
- i.e. *phylogeny (coalescent)*  $\times$  *SIR*

## Example: implementing *TransPhylo* in *outbreaker2*

### *outbreaker* likelihood

- $p(s, t | \alpha, T^{inf}, \kappa, \mu, \pi) = p(T^{inf} | \alpha, \kappa) p(T^{inf} | t) p(s | \alpha, \kappa, \mu) p(\kappa | \pi)$
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### *TransPhylo* likelihood

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- i.e. *phylogeny (coalescent)*  $\times$  *SIR*

Can we combine the two models?

# *TransPhylo* module for *outbreaker2*

### 3 Custom likelihood

In order to calculate the likelihood under the TransPhylo model, we need to (i) extract the transmission tree from the outbreaker2 parameter, (ii) combine this transmission tree with the phylogenetic tree to form a colored tree, and (iii) calculate the likelihood of this colored tree. Step (i) is easy since transmission tree are encoded almost in the same way in TransPhylo and outbreaker2. For step (ii) we have to write the `combine` function which is tedious but not especially interesting (this function is included in this Rnw file but its code is not shown in the pdf). For step (iii) we only need to call the appropriate function of the TransPhylo package which is `probPTreeGivenTree`. During step (ii) messages can arise indicating that the transmission tree and phylogenetic tree are in fact incompatible, in which case the likelihood is returned as -Inf.

```
lik_TransPhylo <- function(data, param) {
  ttree <- list(ttree = chind(param$t.inf, data$dates, param$alpha),
               nam = data$pstree$nam)
  ttrees$ttree(which(is.na(ttrees$ttree[,3])),3) <- 0
  txt <- capture.output(ttree <- combine(ttrees,data$pstree))
  if (length(txt)==0) {
    prob <- probPTreeGivenTree(ttree, neg = 366 * 0.26)
  } else {
    prob <- -Inf
  }
  return(prob)
}

lik_transphylo <- function(date, param, i = NULL, custom_functions = NULL)
{
  ## function (date, param, i = NULL, custom_functions = NULL)

  new_move_tinf <- function(param, data, list_custom_ll = new_model) {
    for (i in 1:date$N) {
      current_ll <- api$cpp_ll_all(data,param, i = NULL, list_custom_ll)
      modif <- sample(c(-100:-1,1:100), 1)
      param$ll.inf[i] <- param$ll.inf[i] + modif
      new_ll <- api$cpp_ll_all(data,param, i = NULL, list_custom_ll)
      if (log10(modif[i]) > log10(ll.inf[i] - current_ll)) {
        param$ll.inf[i] <- param$ll.inf[i] + modif
      }
    }
    return(param)
  }

  new_moves <- custom_moves(t.inf = new_move_tinf)
  new_moves

  ##
  ##
  ## /////////////////////////////////////////////////////////////////// outbreaker movement functions /**
  ##
  ## class: outbreaker_moves list
  ## number of items: 8
  ## /////////////////////////////////////////////////////////////////// movement functions /**
  ## @na
}
```

[Campbell *et al.* (2018) BMC Bioinformatics]

# *TransPhylo* module for *outbreaker2*

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```
lik_TransPhylo <- function(data, param) {
  ttree <- list(ttree = chind(param$t.inf, data$dates, param$alpha),
               nam = data$ptree$nam)
  ttrees$tree(which(is.na(ttrees$ttree[,3]))) <- 0
  txt <- capture.output(ttree <- combine(ttrees,data$ptree))
  if (length(txt)==0) {
    prob <- probPTreeGivenTree(ttree, neg = 366 * 0.26)
  } else {
    prob <- -Inf
  }
  return(prob)
}

## function (date, param, i = NULL, custom_functions = NULL)
## NULL

new_move_tinf <- function(param, data, list_custom_ll = new_model) {
  for (i in 1:date$N) {
    current_ll <- api$pp_ll_all(data,param, i = NULL, list_custom_ll)
    modif <- sample(c(-100:-1,1:100), 1)
    param$ll.inf[i] <- param$ll.inf[i] + modif
    new_ll <- api$pp_ll_all(data,param, i = NULL, list_custom_ll)
    if (log10(modif[i]) > log10(ll - current_ll)) {
      param$ll.inf[i] <- param$ll.inf[i] + modif
    }
  }
  return(param)
}

new_moves <- custom_moves(t.inf = new_move_tinf)
new_moves

## 
## ///////////////////////////////////////////////////////////////////
## 
## class: outbreaker_moves list
## number of items: 8
## 
## // movement functions //
## 
## 
```

likelihood

[Campbell *et al.* (2018) BMC Bioinformatics]

# *TransPhylo* module for *outbreaker2*

### 3 Custom likelihood

In order to calculate the likelihood under the TransPhylo model, we need to (i) extract the transmission tree from the outbreaker2 parameter, (ii) combine this transmission tree with the phylogenetic tree to form a colored tree, and (iii) calculate the likelihood of this colored tree. Step (i) is easy since transmission tree are encoded almost in the same way in TransPhylo and outbreaker2. For step (ii) we have to write the `combine` function which is tedious but not especially interesting (this function is included in this Rnw file but its code is not shown in the pdf). For step (iii) we only need to call the appropriate function of the TransPhylo package which is `probPTreeGivenTree`. During step (ii) messages can arise indicating that the transmission tree and phylogenetic tree are in fact incompatible, in which case the likelihood is returned as -Inf.

```
lik_TransPhylo <- function(data, param) {
  ttree <- list(ttree = chind(param$t.inf, data$dates, param$alpha),
               nam = data$ptree$nam)
  ttree$tree[[which(is.na(ttree$tree[,3]))]] <- 0
  txt <- capture.output(ctree <- combine(ttree, data$ptree))
  if (length(txt)==0) {
    prob <- probPTreeGivenTree(ctree, neg = 366 * 0.26)
  } else {
    prob <- -Inf
  }
  return(prob)
}
```

likelihood

### movement function

```
args(api$cpp_ll_all)
## function (date, param, i = NULL, custom_functions = NULL)
## NULL

new_move_tinf <- function(param, data, list_custom_ll = new_model) {
  for (i in 1:date$N) {
    current_ll <- api$cpp_ll_all(data, param, i = NULL, list_custom_ll)
    modif <- sample(c(-100:-1, 1:100), 1)
    param$inf[i] <- param$inf[i] + modif
    new_ll <- api$cpp_ll_all(data, param, i = NULL, list_custom_ll)
    if (log(new_ll) > log(current_ll)) {
      param$inf[i] <- param$inf[i] + modif
    }
  }
  return(param)
}

new_moves <- custom_moves(t_inf = new_move_tinf)
new_moves

##
## //////////////////////////////////////////////////////////////////
## class: outbreaker_moves list
## number of items: 8
## //////////////////////////////////////////////////////////////////
## movement functions //
## See
```

[Campbell *et al.* (2018) BMC Bioinformatics]

# *TransPhylo* module for *outbreaker2*

### 3 Custom likelihood

In order to calculate the likelihood under the TransPhylo model, we need to (i) extract the transmission tree from the outbreaker2 parameter, (ii) combine this transmission tree with the phylogenetic tree to form a colored tree, and (iii) calculate the likelihood of this colored tree. Step (i) is easy since transmission tree are encoded almost in the same way in TransPhylo and outbreaker2. For step (ii) we have to write the `combine` function which is tedious but not especially interesting (this function is included in this Rnw file but its code is not shown in the pdf). For step (iii) we only need to call the appropriate function of the TransPhylo package which is `probPTreeGivenTree`. During step (ii) messages can arise indicating that the transmission tree and phylogenetic tree are in fact incompatible, in which case the likelihood is returned as -Inf.

```
lik_TransPhylo <- function(data, param) {
  ttree <- list(ttree = chind(param$t.inf, data$dates, param$alpha),
               nam = data$ptree$nam)
  ttree$trees[[which(is.na(ttree$trees[[3]]))]] <- 0
  txt <- capture.output(ctree <- combine(ttree, data$ptree))
  if (length(txt) == 0) {
    prob <- probPTreeGivenTree(ctree, neg = 366 * 0.26)
  } else {
    prob <- -Inf
  }
  return(prob)
}
```

likelihood

Total: 25 lines of R

*outbreaker2*: 7,500 lines of R/C++

Code difference: 0.3%

### movement function

```
args(api$cpp_ll_all)
## function (date, param, i = NULL, custom_functions = NULL)
## NULL

new_move_tinf <- function(param, data, list_custom_ll = new_model) {
  for (i in 1:dates$N) {
    current_ll <- api$cpp_ll_all(data, param, i = NULL, list_custom_ll)
    modif <- sample(c(-100:-1, 1:100), 1)
    param$inf[[i]] <- param$inf[[i]] + modif
    new_ll <- api$cpp_ll_all(data, param, i = NULL, list_custom_ll)
    if (log(modif[[i]]) > log(new_ll[[i]] - current_ll[[i]])) {
      param$inf[[i]] <- param$inf[[i]] + modif
    }
  }
  return(param)
}

new_moves <- custom_moves(t_inf = new_move_tinf)
new_moves

##
## ///////////////////////////////////////////////////////////////////
## class: outbreaker_moves list
## number of items: 8
## ///////////////////////////////////////////////////////////////////
## movement functions //
## @name
```

[Campbell *et al.* (2018) BMC Bioinformatics]

# *TransPhylo* module for *outbreaker2*

## 3 Custom likelihood

In order to calculate the likelihood under the TransPhylo model, we need to (i) extract the transmission tree from the *outbreaker2* parameter, (ii) combine this transmission tree with the phylogenetic tree to form a colored tree, and (iii) calculate the likelihood of this colored tree. Step (i) is easy since transmission tree are encoded as a list in *outbreaker2* and phylogenetic tree in *TransPhylo*. Step (ii) we have to write a simple function to do this. Step (iii) is especially interesting (this function is in `likelihood.R`). In *outbreaker2*, the likelihood function in `likelihood.R` only need to call the appropriate function in `outbreaker2` to get the likelihood. In *TransPhylo*, the likelihood needs to handle (i) messages can arise indicating that the transmission tree and phylogenetic tree are in fact in conflict, and (ii) in the case the likelihood is returned as -Inf.

```
lik_TransPhylo <- function(data, param) {
  ttree <- list(ttree = chid(param$inf, data$data, param$alpha),
               ann = data$tree$ann)
  ttrees@tree[which(is.na(ttrees@tree[,3]))] <- 0
  ttrees@tree <- capture.output(ttree <- combine(ttrees,data$ptree))
  if (length(ttree)==0) {
    prob <- 0.0001
  } else {
    prob <- 1
  }
  return(prob)
}
```

likelihood

Total: 25 lines of R

*outbreaker2*: 7,500 lines of R/C++

**Code difference: 0.3%**

[Campbell *et al.* (2018) BMC Bioinformatics]

New stuff

Old wheel

movement

param, 1 ~ HSOL, cys

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param, 218 ~ HSOL, cys

param, 219 ~ HSOL, cys

param, 220 ~ HSOL, cys

param, 221 ~ HSOL, cys

param, 222 ~ HSOL, cys

param, 223 ~ HSOL, cys

param, 224 ~ HSOL, cys

param, 225 ~ HSOL, cys

param, 226 ~ HSOL, cys

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param, 231 ~ HSOL, cys

param, 232 ~ HSOL, cys

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param, 236 ~ HSOL, cys

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param, 238 ~ HSOL, cys

param, 239 ~ HSOL, cys

param, 240 ~ HSOL, cys

param, 241 ~ HSOL, cys

param, 242 ~ HSOL, cys

param, 243 ~ HSOL, cys

param, 244 ~ HSOL, cys

param, 245 ~ HSOL, cys

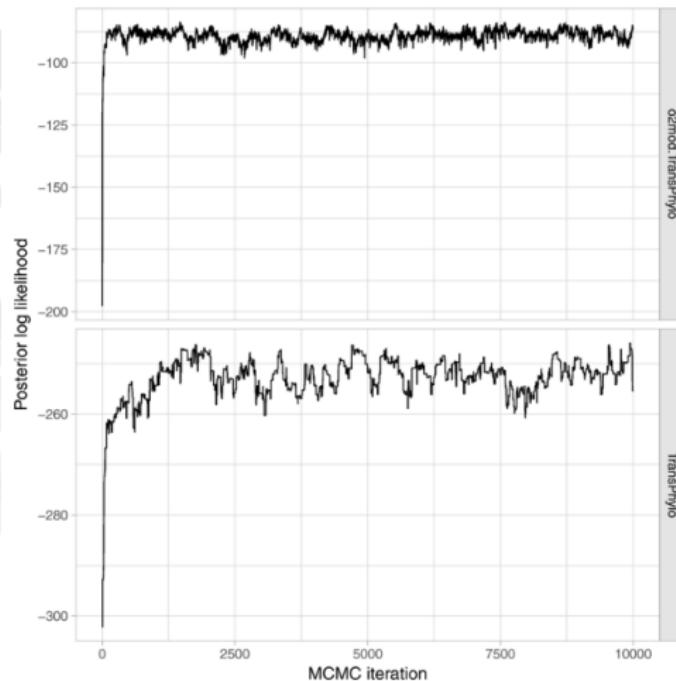
param, 246 ~ HSOL, cys

param, 247 ~ HSOL, cys

param, 248 ~ HSOL, cys

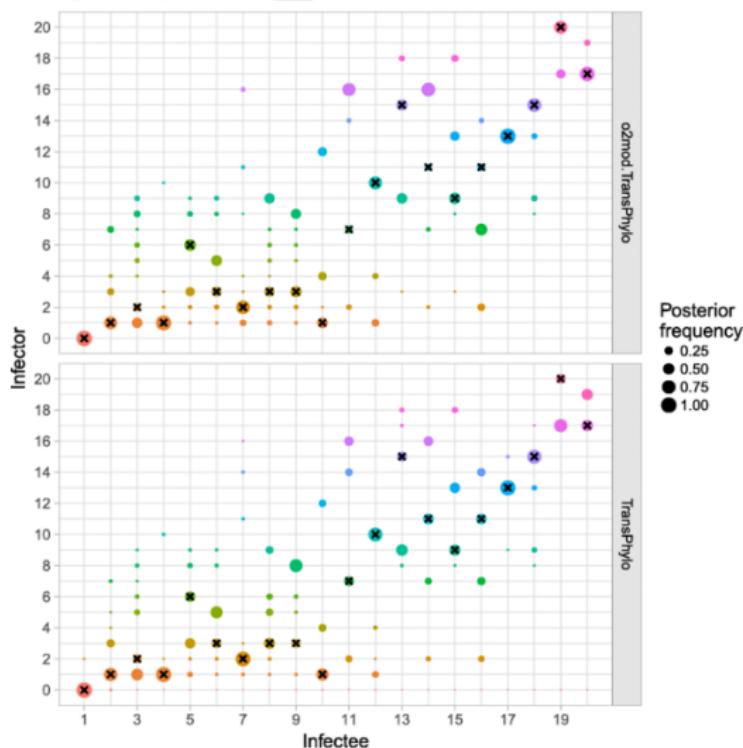
param, 249

# Transphylo module results (1/2): convergence



[Campbell *et al.* (2018) BMC Bioinformatics]

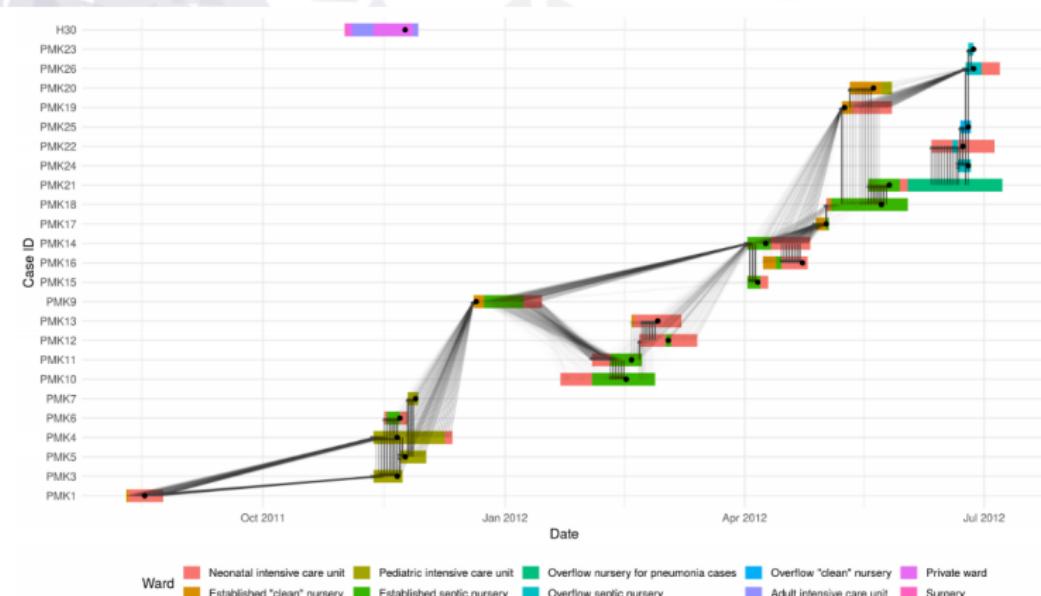
## Transphylo module results (2/2): trees



[Campbell *et al.* (2018) BMC Bioinformatics]

# New modules and ongoing work

Contact data, nosocomial transmission, haplotype model, spatial model, ...



[Campbell et al. (in prep)]

# Looking ahead



- **common platform**: good opportunity for increased collaborations and comparisons of methods

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- **transmission trees vs transmission clusters**

# Who infects whom: when do we care?



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# Who infects whom: when do we care?

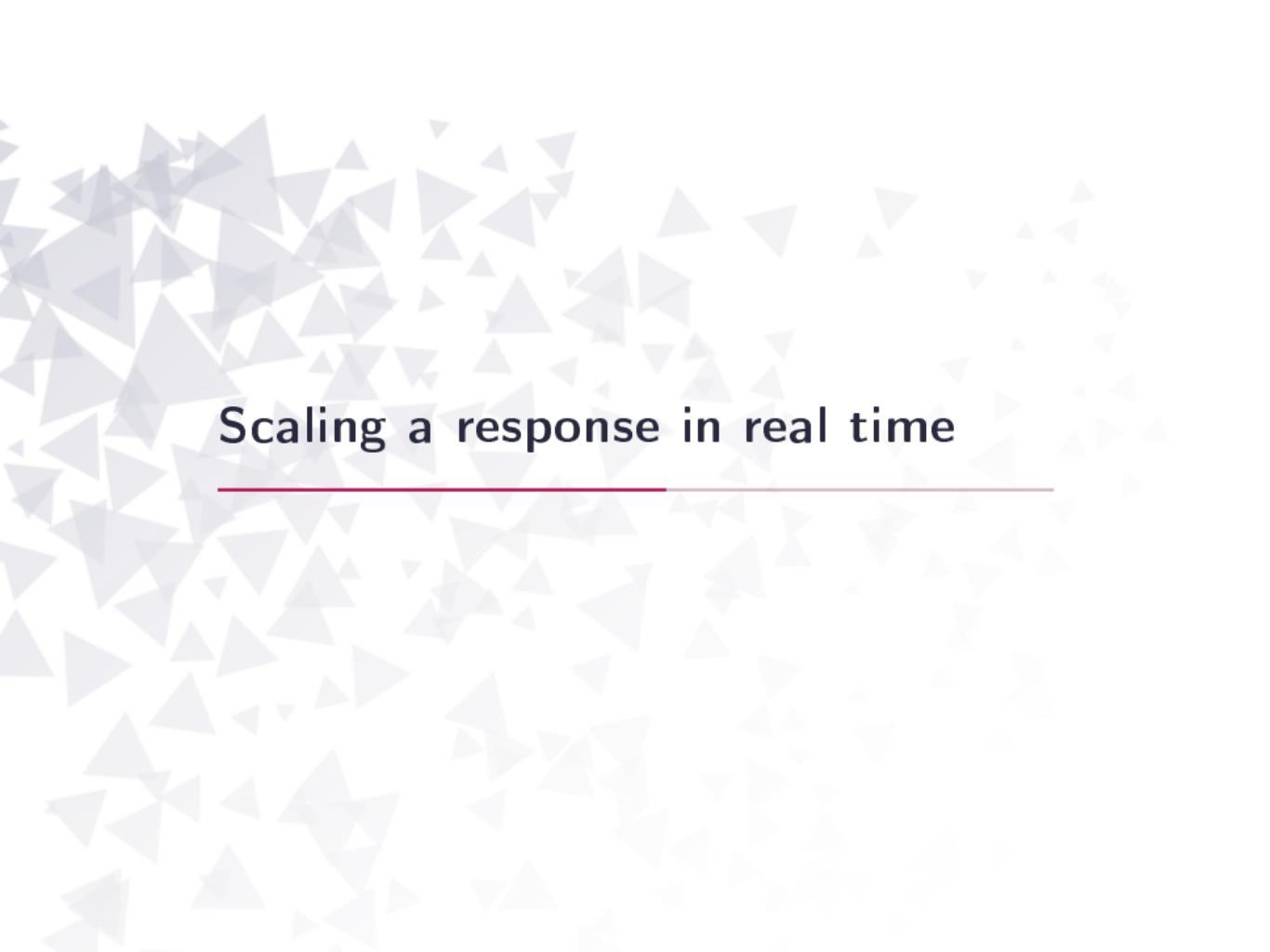


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# Who infects whom: when do we care?



- complex methods, WGS data costly: **is it worth it?**
- in general, not useful for **forecasting**
- useful to detect **multiple introductions** or **superspreading**
- complement **exposure / contact tracing** data

The background of the slide features a large number of small, light-gray triangles of various sizes scattered across the white surface, creating a subtle geometric pattern.

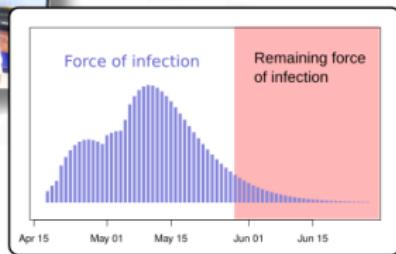
## Scaling a response in real time

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# Ebola outbreak, Likati (DRC) 2017

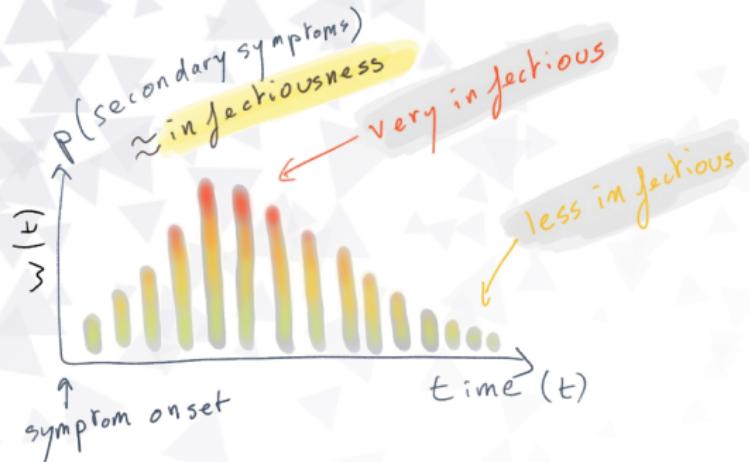


- EVD outbreak May 2017
- contact data visualisation tools used in contact tracing
- simple model informed response (scaling)
- end: 2nd July 2017



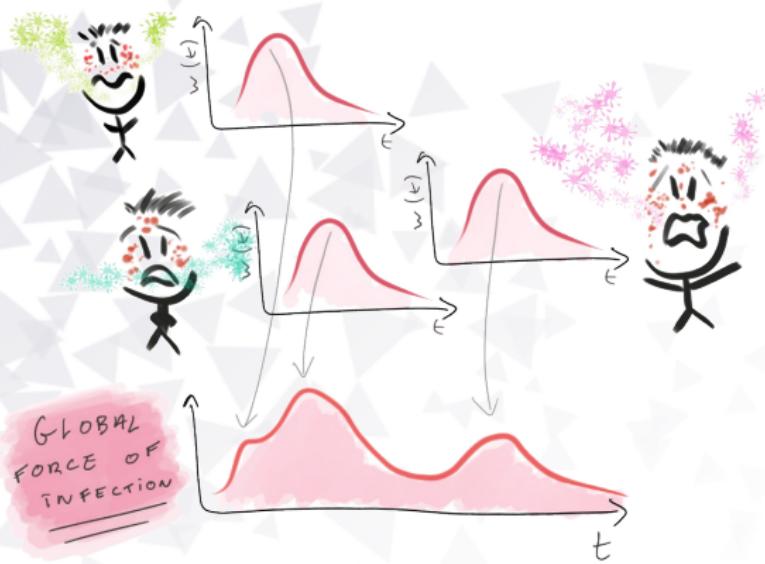
# Individual infectiousness over time

Serial interval: delay between symptom onset in infector and infectees



Indicates when we expect new cases, if there are any.

# A “simple” branching process model



$$y_t \sim \mathcal{P}(\lambda_t) \quad ; \quad \lambda_t = R_0 \times \sum_i w(t - t_i)$$

$y_t$ : incidence at time  $t$ ;  $\mathcal{P}()$ : Poisson distribution;  $\lambda_t$ : **global force of infection**;  $w()$ : serial interval distribution;  $t_i$ : date of symptom onset

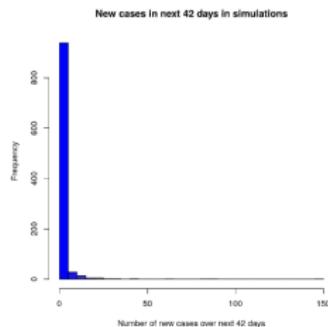
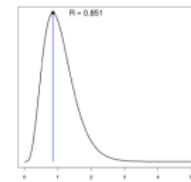
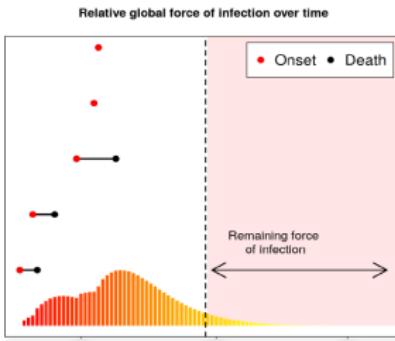
# A model for short-term forecasting



1. estimate  $R$  from incidence  $y_1, \dots, y_t$  until time  $t$
2. simulate incidence  $y_{t+1} \sim \mathcal{P}(\lambda_{t+1})$
3. increase  $t$  by one day, repeat

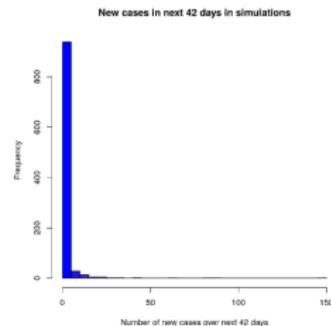
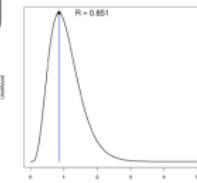
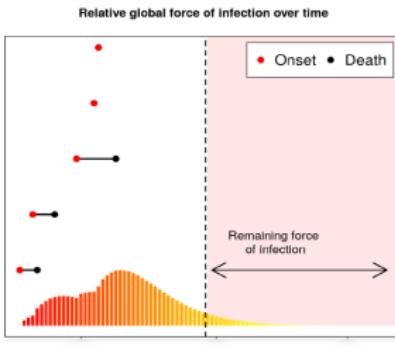
# Scaling the response in real-time

Estimating remaining force of infection,  
transmissibility ( $R$ ), predicting new cases



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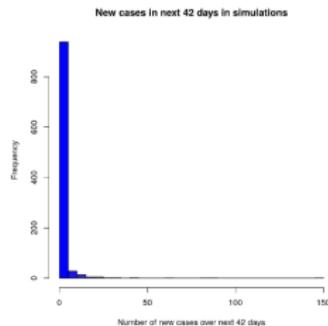
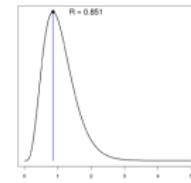
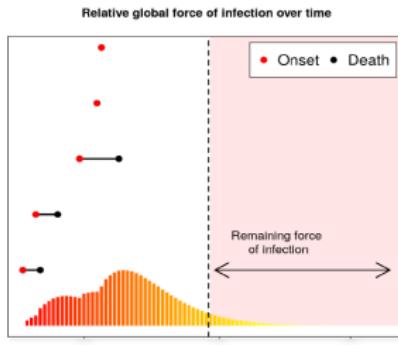
Estimating remaining force of infection,  
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Despite uncertainty in  $R_0$ , new cases were unlikely.

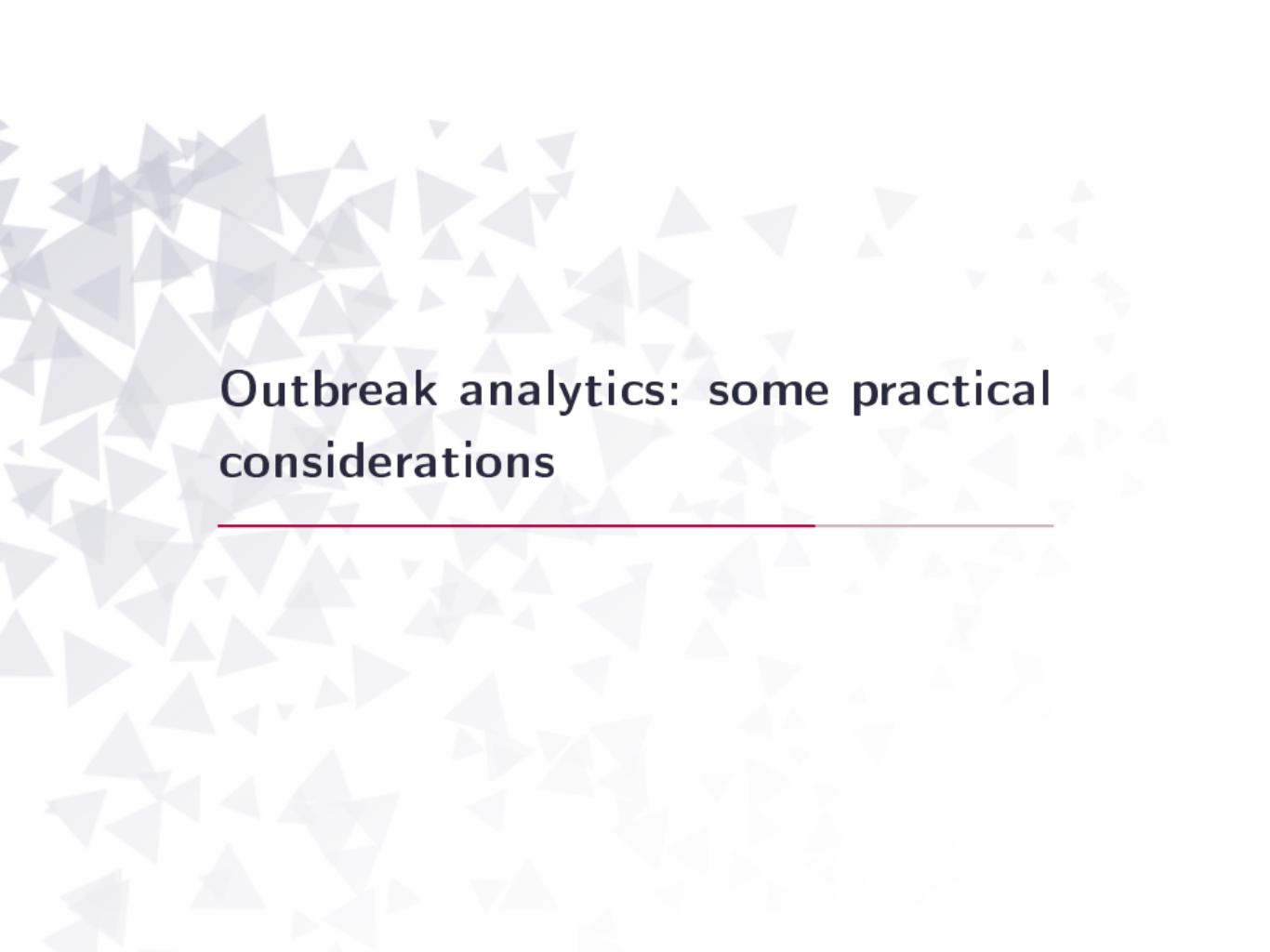
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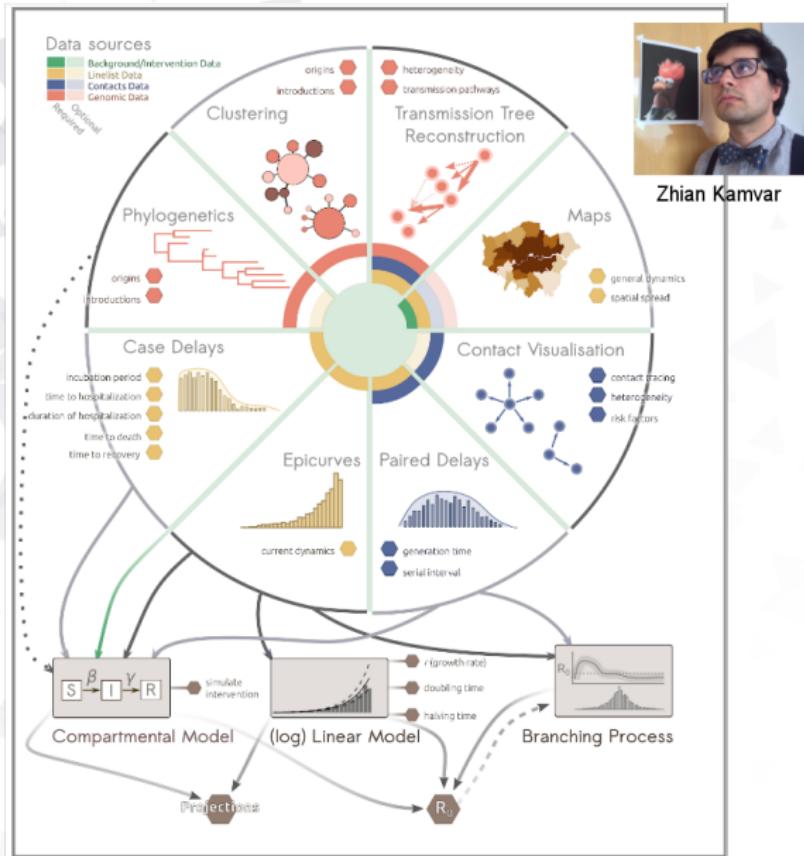
Discouraged scaling up in resource-limited context.



## **Outbreak analytics: some practical considerations**

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# Cost-effective analyses: data needs vs actionable intel



# Centralised analyses, distributed delays



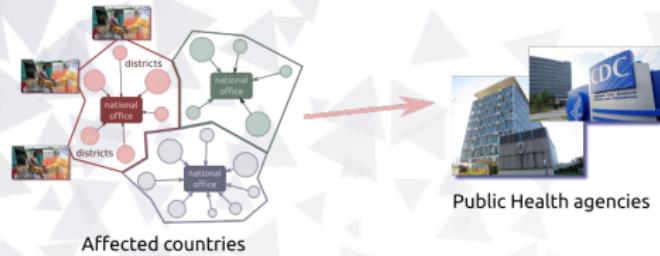
# Centralised analyses, distributed delays



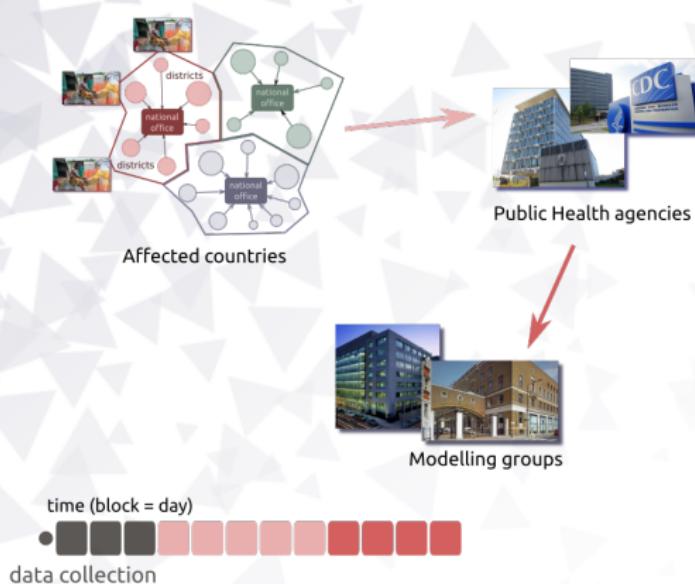
# Centralised analyses, distributed delays



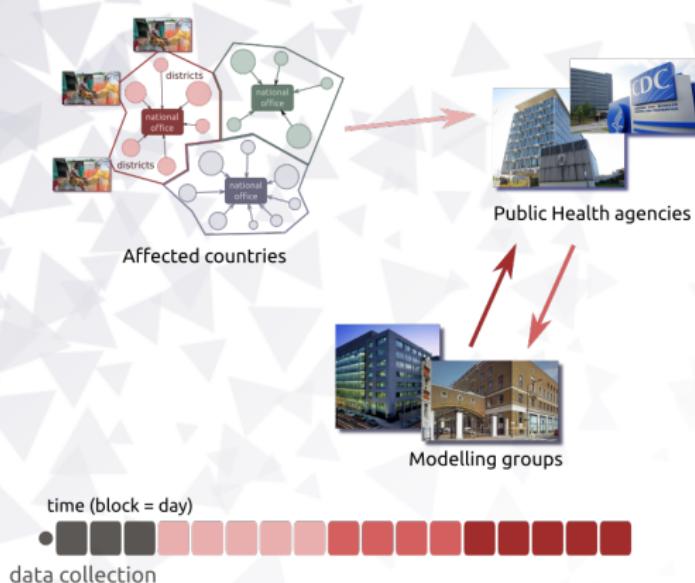
# Centralised analyses, distributed delays



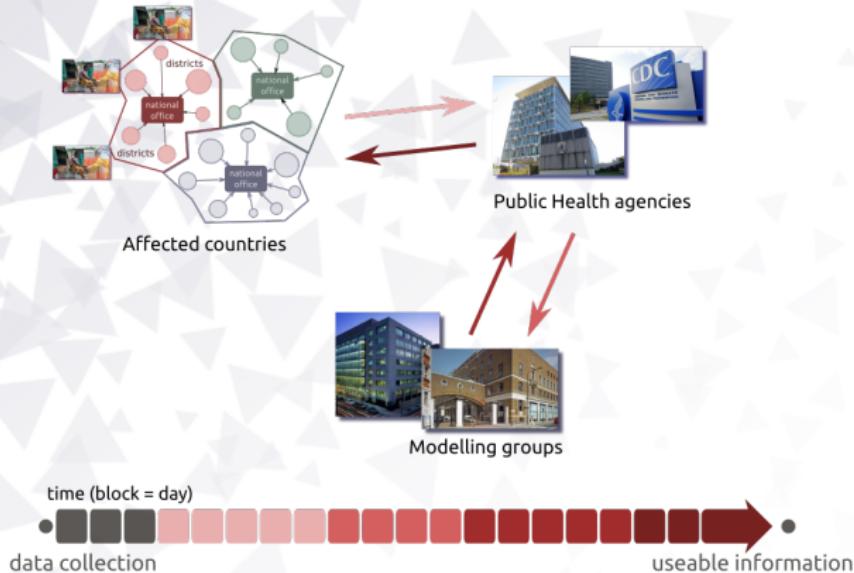
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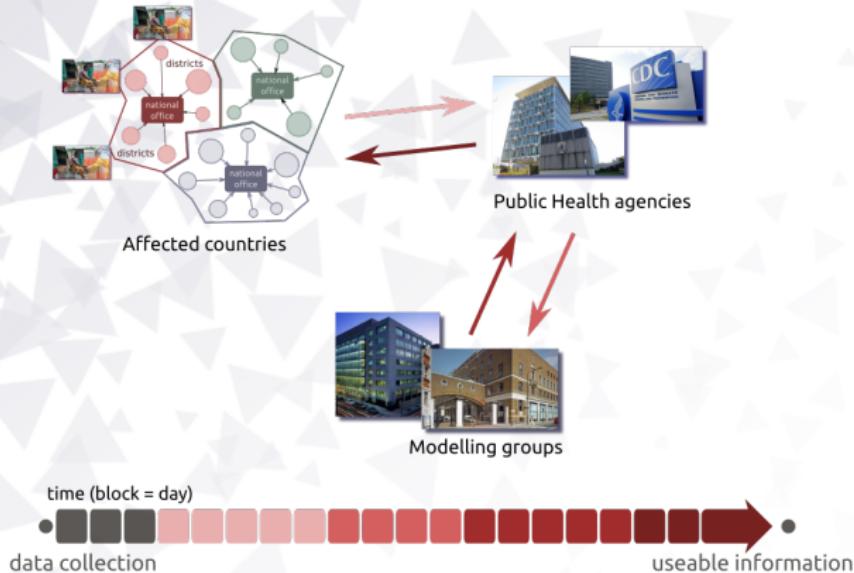
# Centralised analyses, distributed delays



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# Centralised analyses, distributed delays



Timeliness is key: need to bring analytics to the field

Bringing analytics resources where they are needed

# RECON

*www.repidemicsconsortium.org*

- an NGO for free, open **health crisis analytics**
- 100-150 subscribers, ~30 active members

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- **10 packages released**, ~15 in development
- **short courses** with partner institutions (CDC, MSF, WHO, EAN, ...)
- support **field deployment**

## Thanks to:

- **Organisers:** J & J
- **Collaborators:** Finlay Campbell, Anne Cori, Pierre Nouvellet, Zhian Kamvar, Stephen Baker, Amrish Baidjoe, Neil Ferguson, Dan Bausch, Jimmy Whitworth, Bayard Roberts, John Edmunds
- **Groups:** WHO Ebola Likati Response Team
- **Funding:** GCRF project RECAP (ES/P010873/1), UK PH RST, HPRU-NIHR, MRC

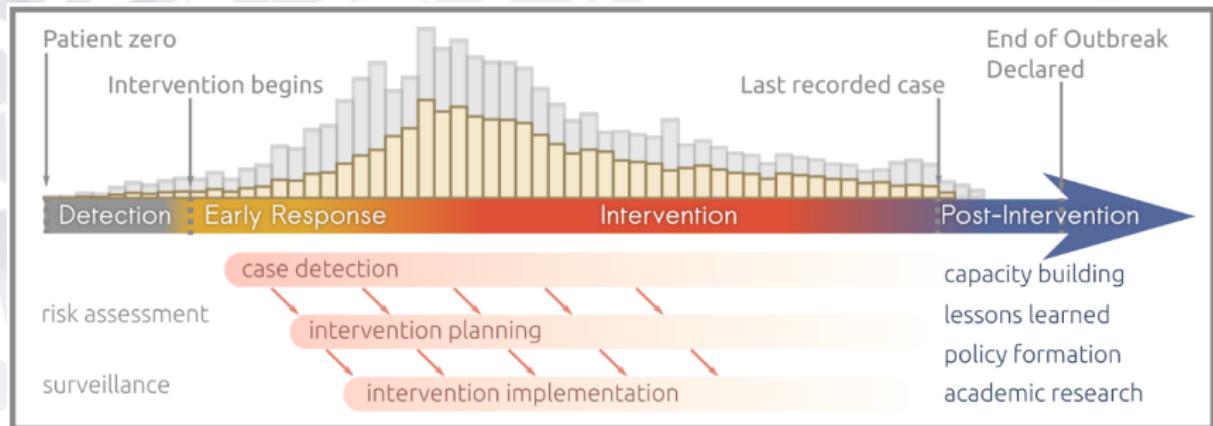
Get these slides at:



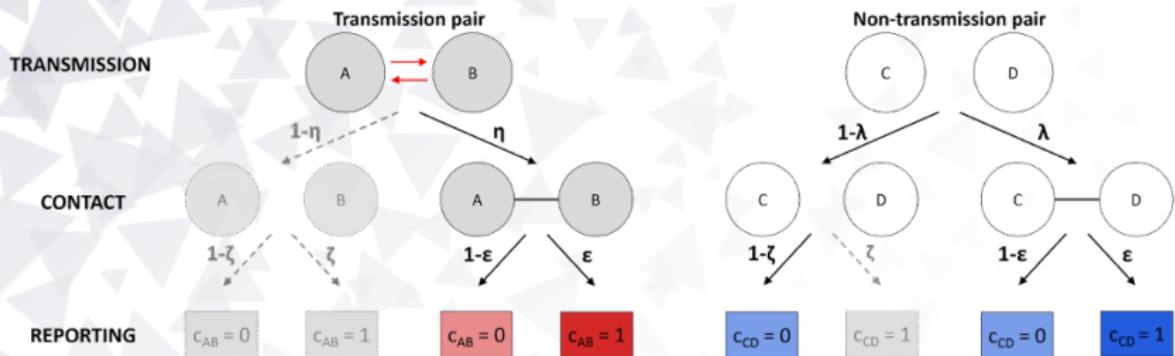
RECON

[www.repidemicsconsortium.org](http://www.repidemicsconsortium.org)

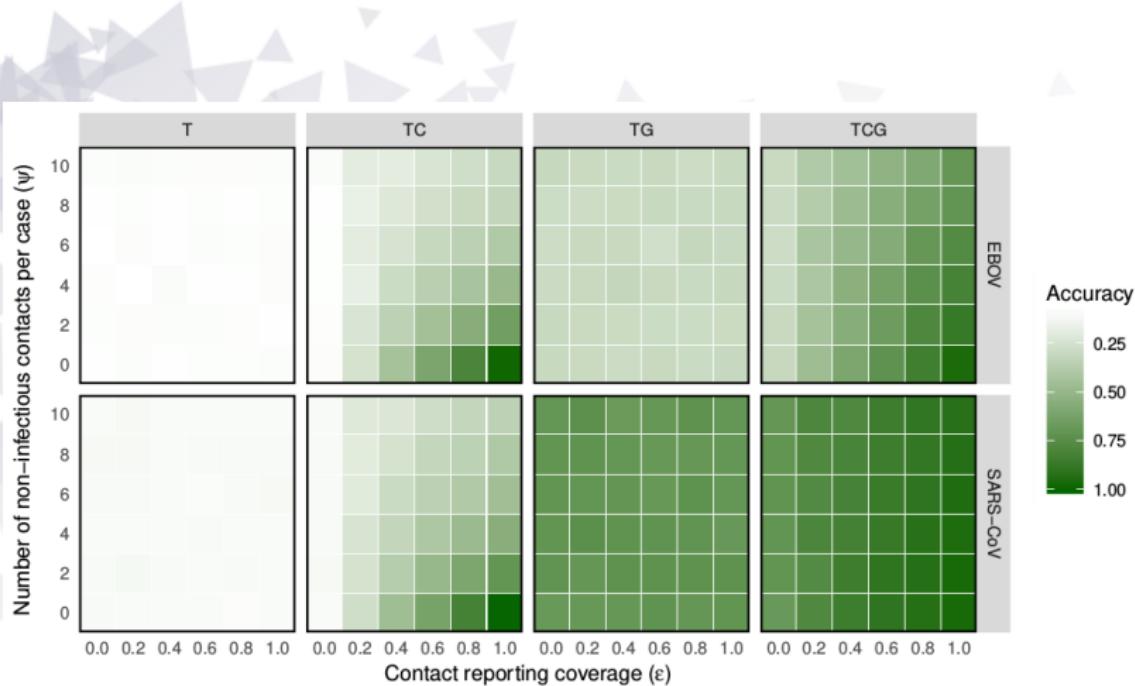
# Outbreak analytics timeline



# Contact model: how it works

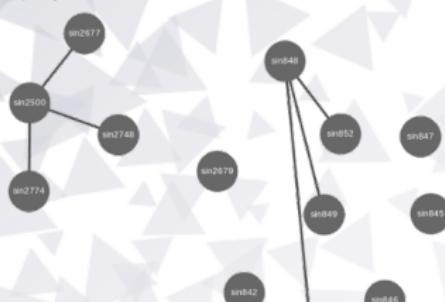


# Contact model: results (1/2)

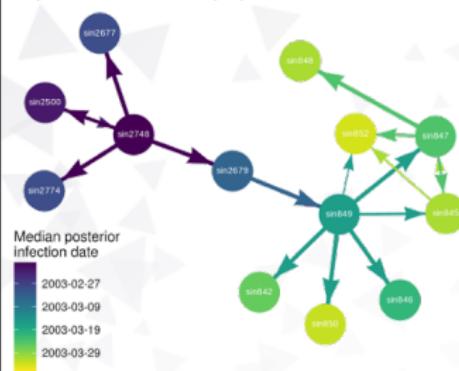


# Contact model: results (2/2)

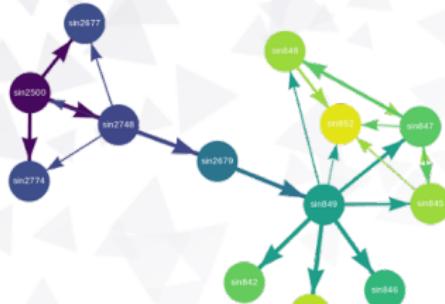
A) Reported contacts



B) Posterior ancestries (TG)



C) Posterior ancestries (TCG,  $\lambda = 1e-4$ )



D) Posterior ancestries (TCG,  $\lambda = 0$ )

