COMBACTE-CDI

State of the art on *Clostridium difficile*

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AMSTERDAM, THE NETHERLANDS

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UMC Utrecht

COMBACTE– *Clostridium difficile* Infection

- COMBACTE-CDI aims to develop a detailed understanding of the epidemiology and clinical impact of CDI

- The project's objectives are to:
  - Align and understand the unmet public health needs relating to CDI
  - Identify and quantify the direct and long-term burden of CDI on healthcare systems
  - Create an EU research platform that will address unmet research questions and provide support for potential proof-of-concept studies of new prevention and treatment strategies for CDI

COMBACTE-CDI aligns clinical/research consortia that have developed independently, one focusing on CDI and the other on AMR, with the CDI-related expertise of 6 EFPIA partners

Ambition

- Better quantification of the burden of CDI disease in EU
  - Integrating data on hospital and community-based patients

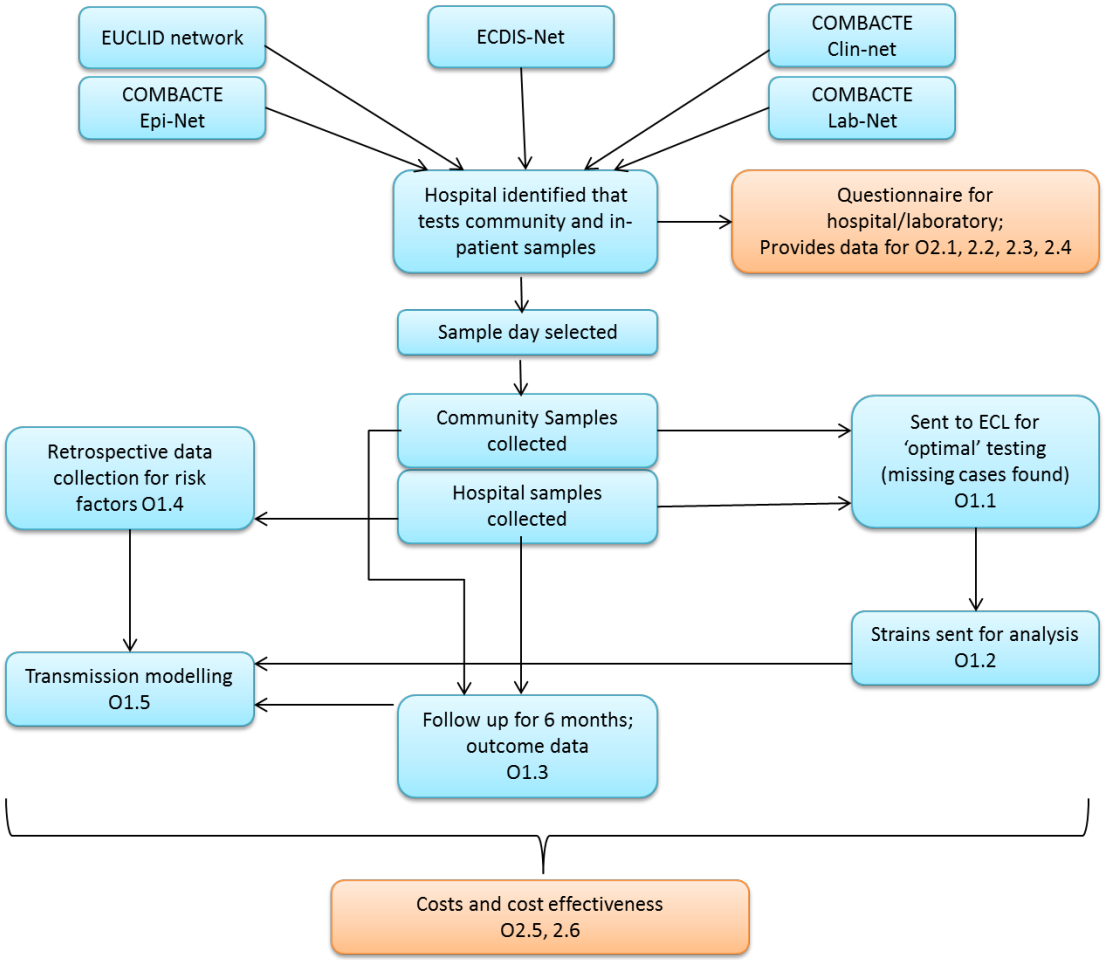
- Accurate determination of;
  - The prevalence of CDI, using comparative diagnostics
  - Molecular epidemiology of *C. difficile*
  - Successful clonal lineages, by transmission modeling

- Collect information on demographics, clinical treatment and outcomes;
  - Aid better design, conduct and interpretation of trials for prevention and treatment of CDI

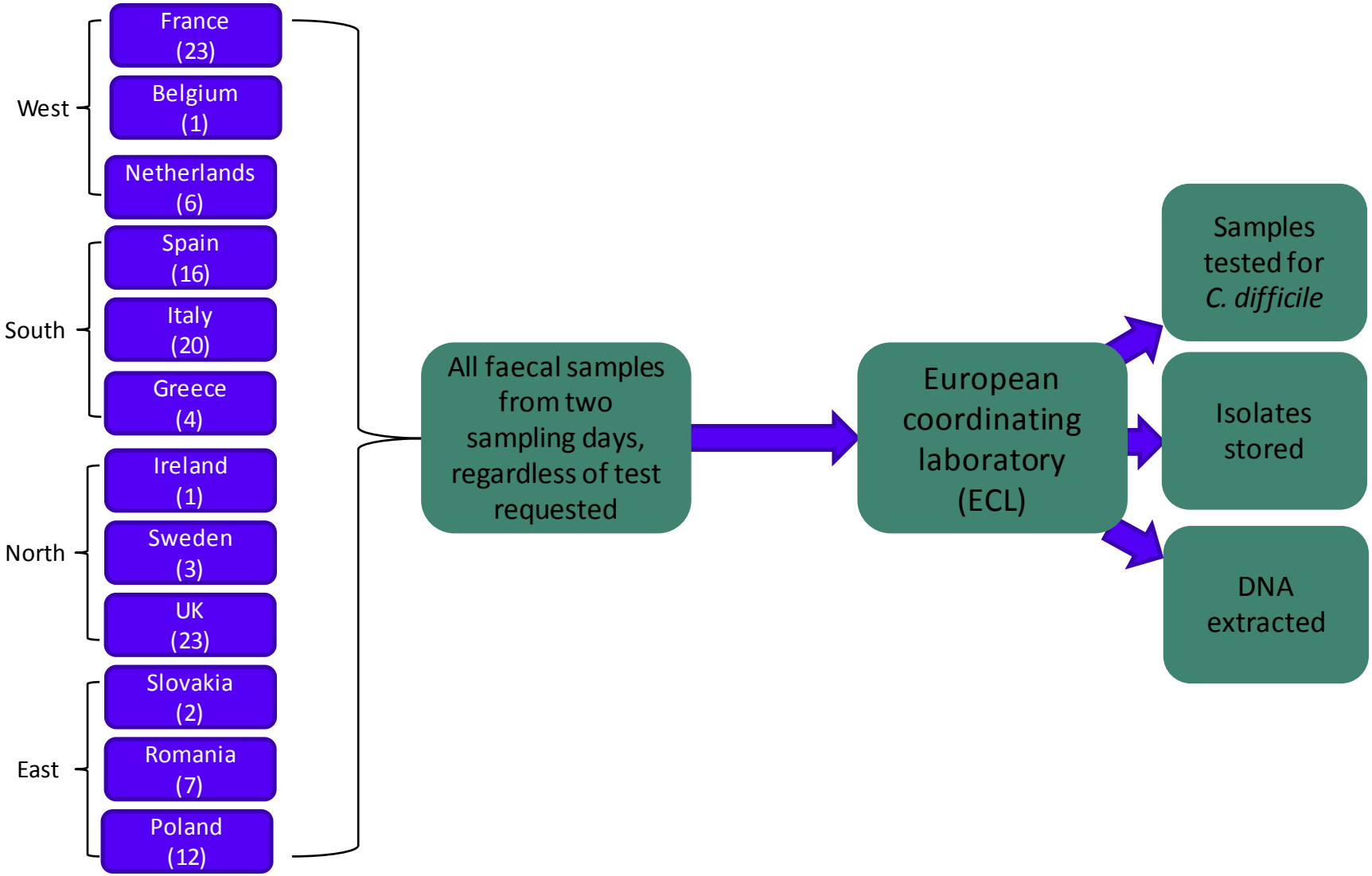
- Quantify the economic impact of novel CDI treatment options and perform transmission dynamic model-based (cost-)effectiveness evaluations of interventions (e.g., antimicrobial stewardship) for CDI

- Align all the data to develop a best-practice model for *C. difficile* infection prevention, diagnosis, treatment and surveillance

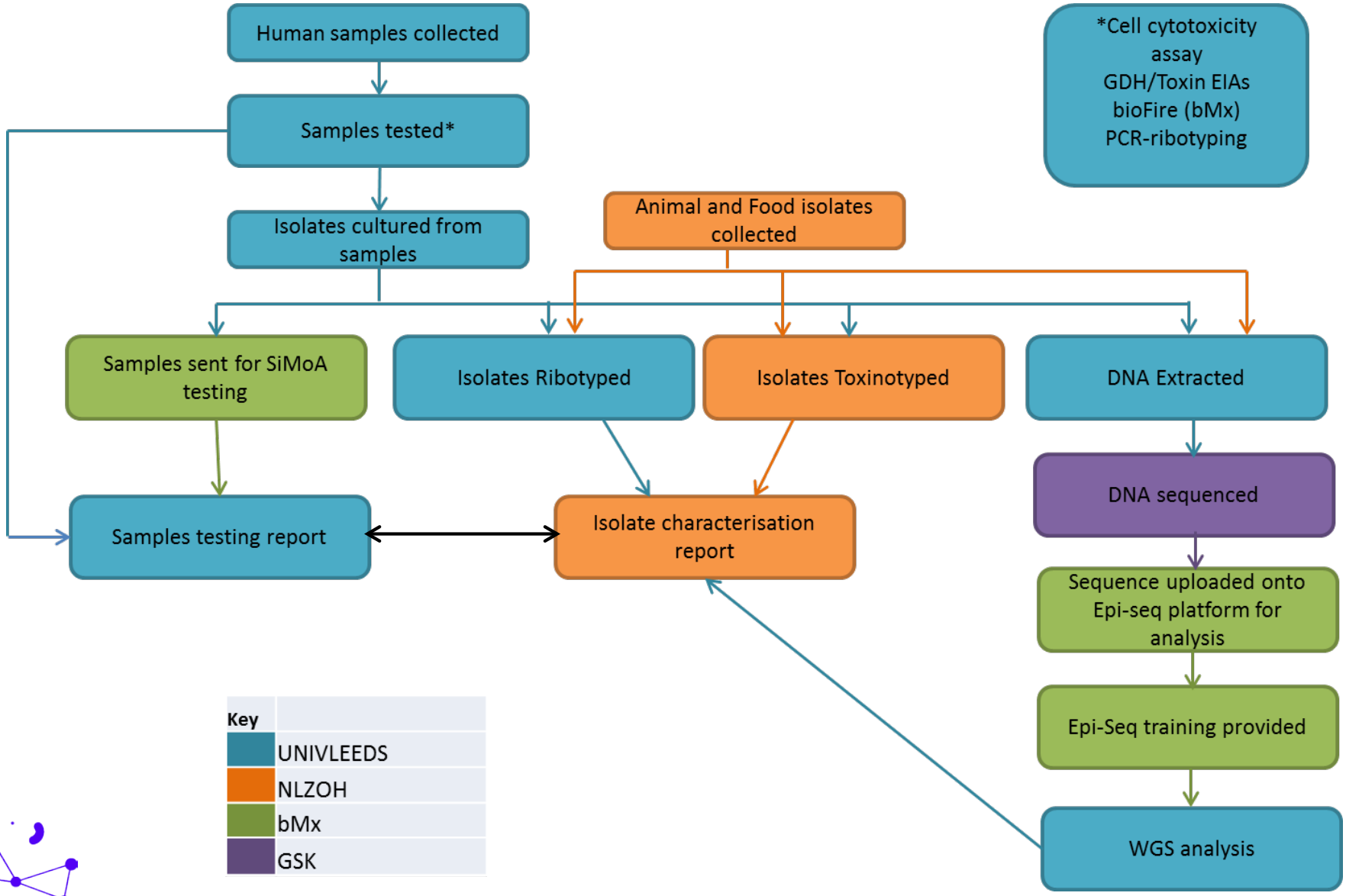
Integrated project plan



Sample collection study

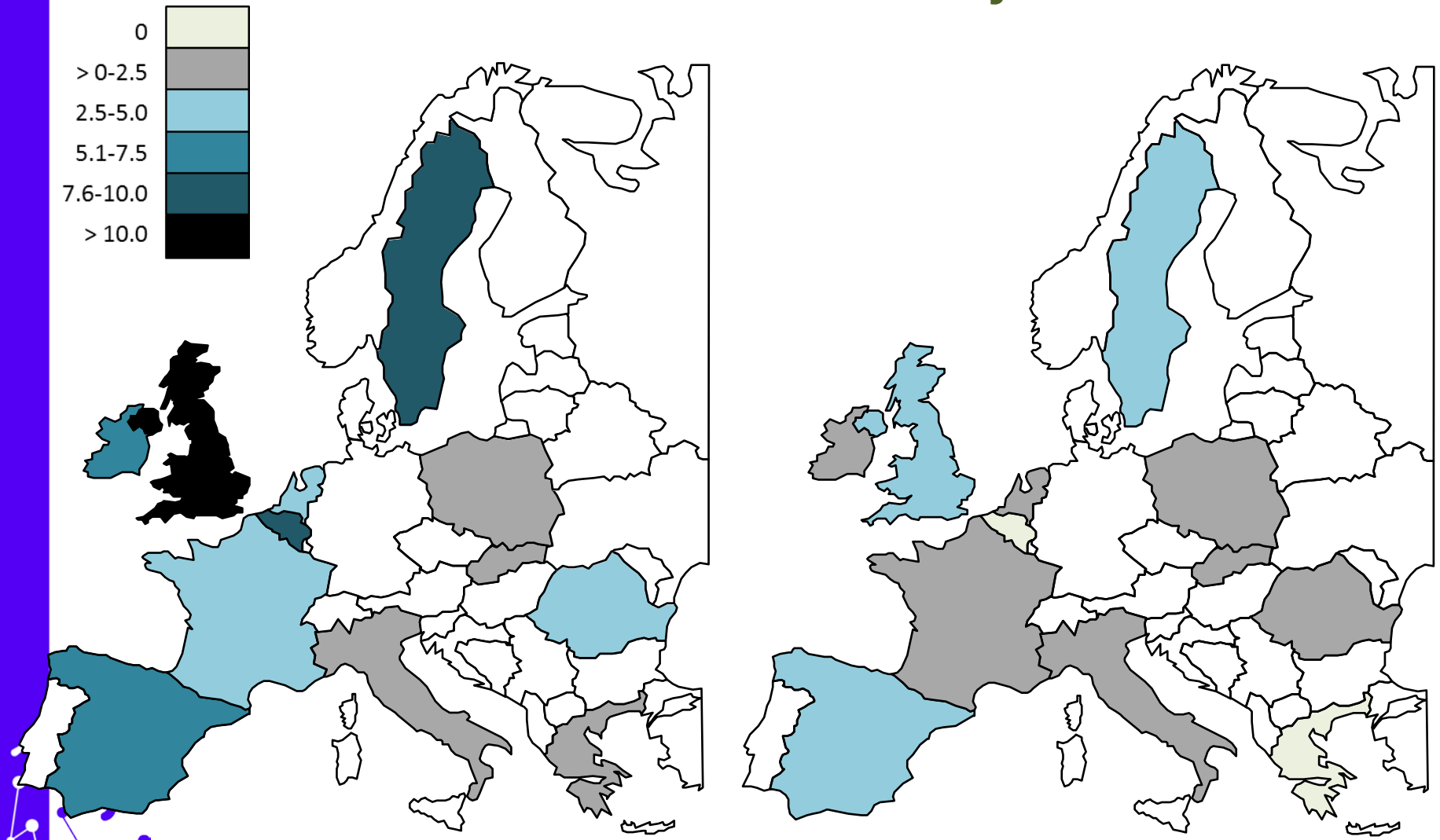


Sample/isolate testing- a collaborative affair



Testing rates

Number of tests/site/day

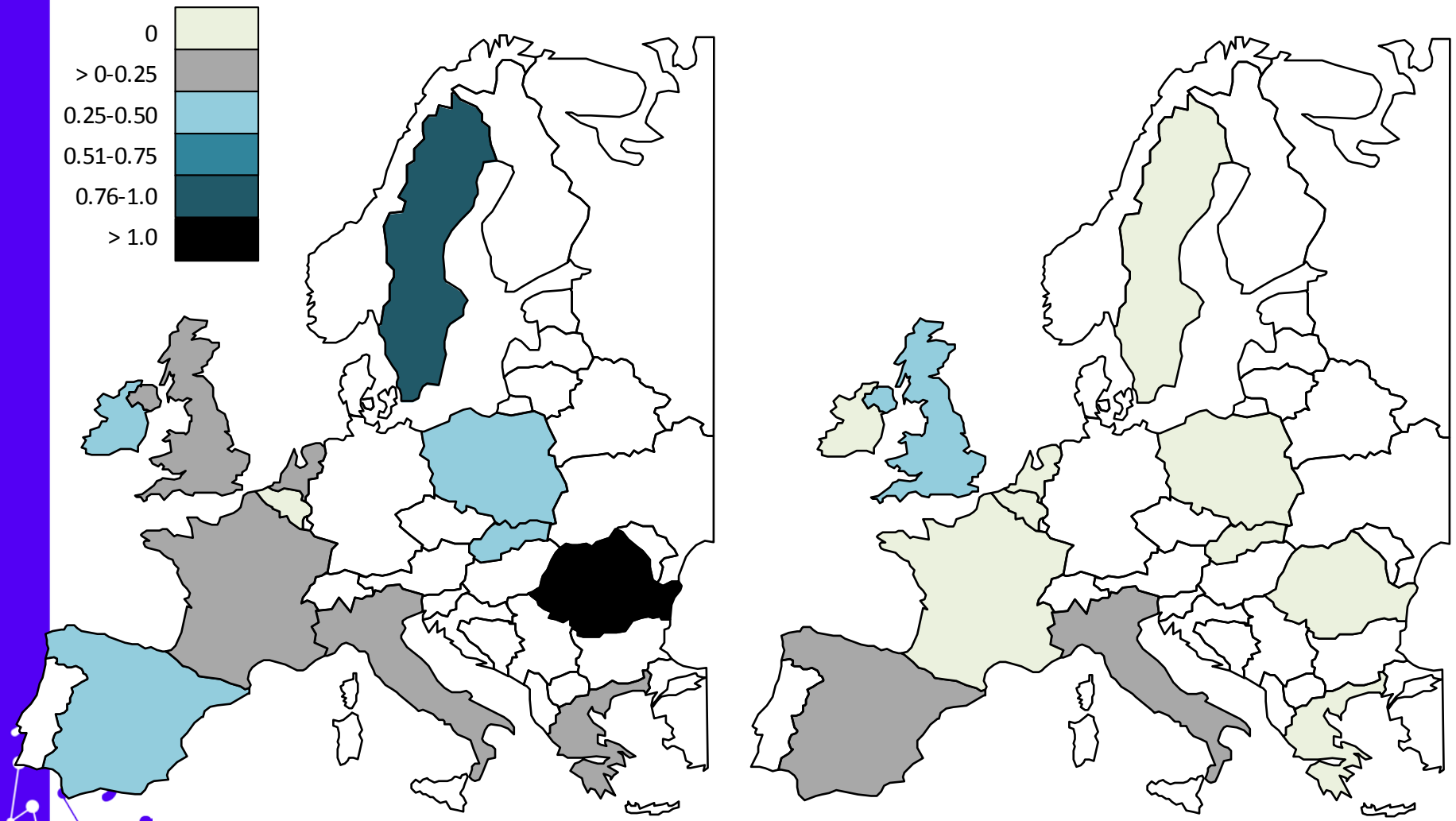


Hospital

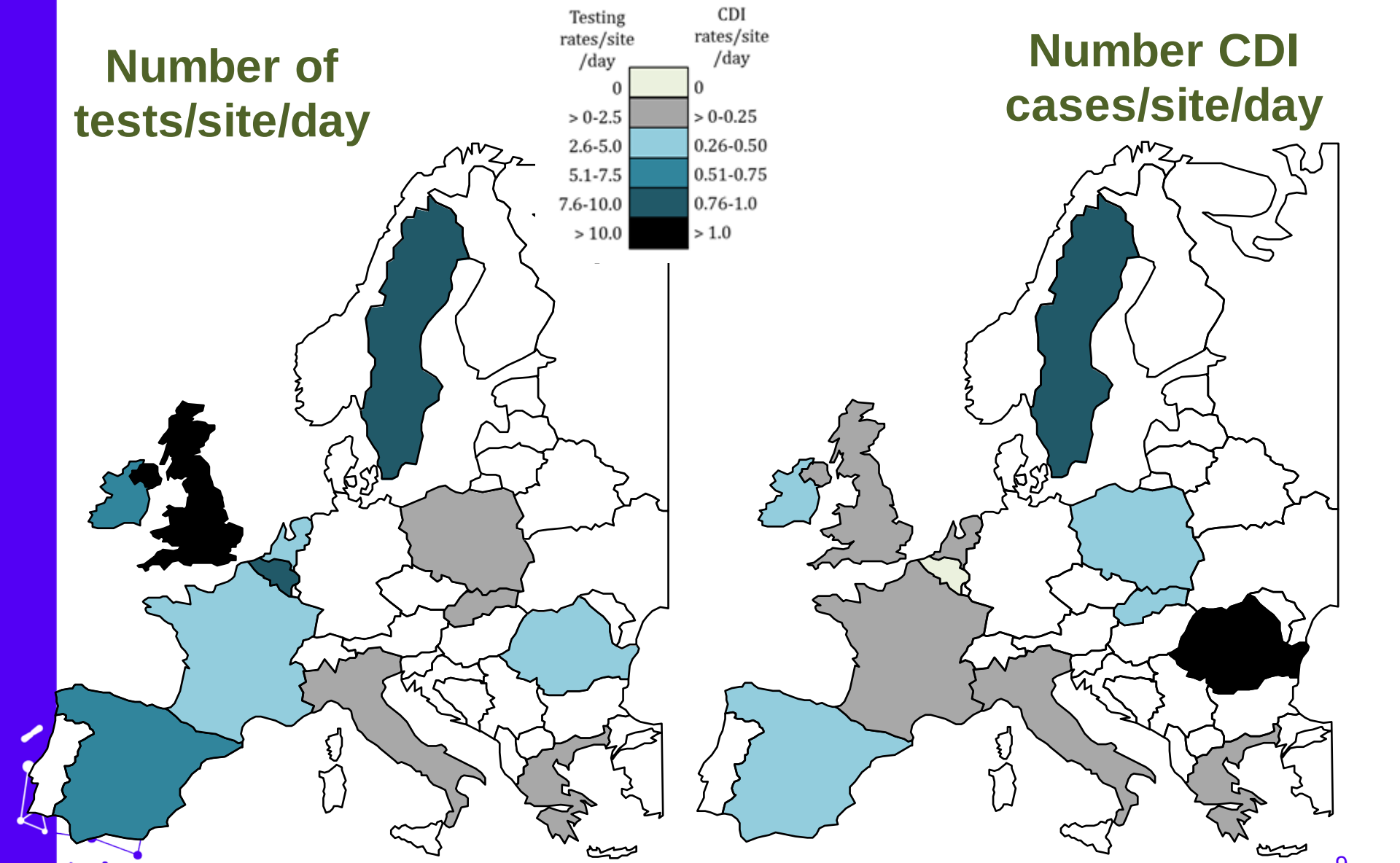
Community

CDI rates – based on ECL testing results

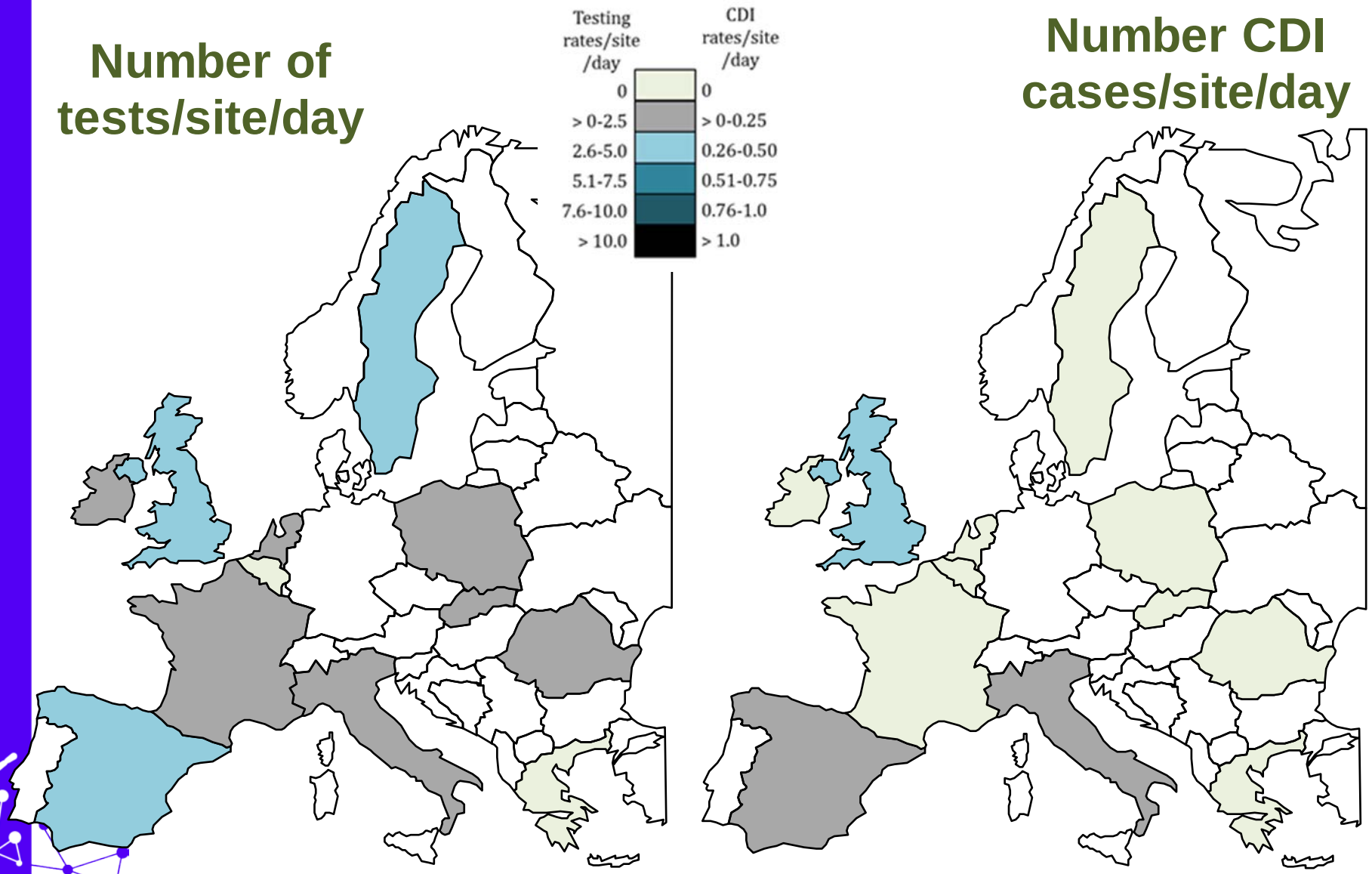
Number of CDI cases/site/day



Hospital testing and CDI rates

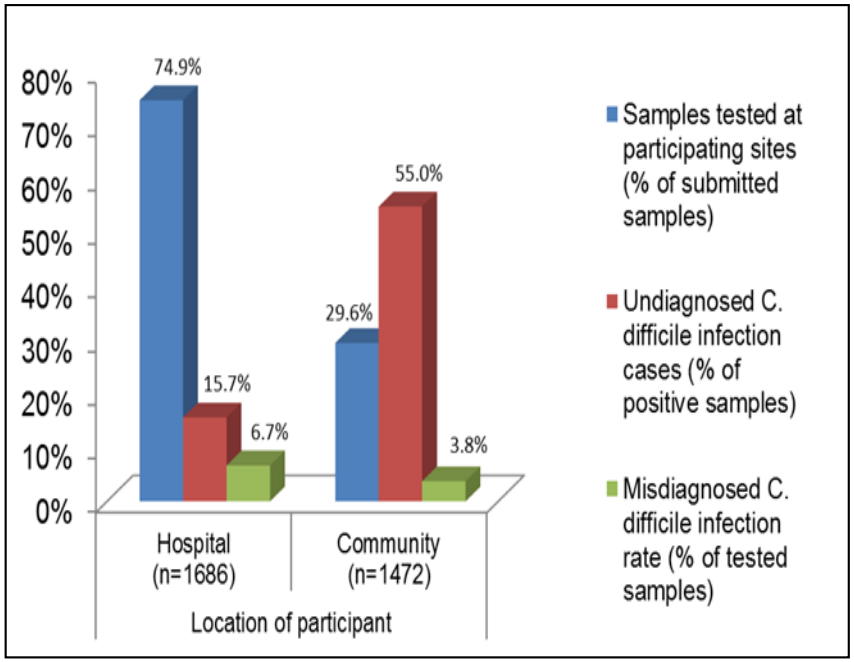


Community testing and CDI rates



Missed cases

- Testing ALL samples submitted enabled detection of missed cases
- There are a higher proportion of undiagnosed cases in the community than in the hospital
  - 55% community cases missed
  - 15.7% hospital cases missed
- This is a unique and novel finding and highlights the lack of suspicion in the community for CDI
- This knowledge may impact on diagnostic guidelines, which largely focus on testing of hospitalised individuals

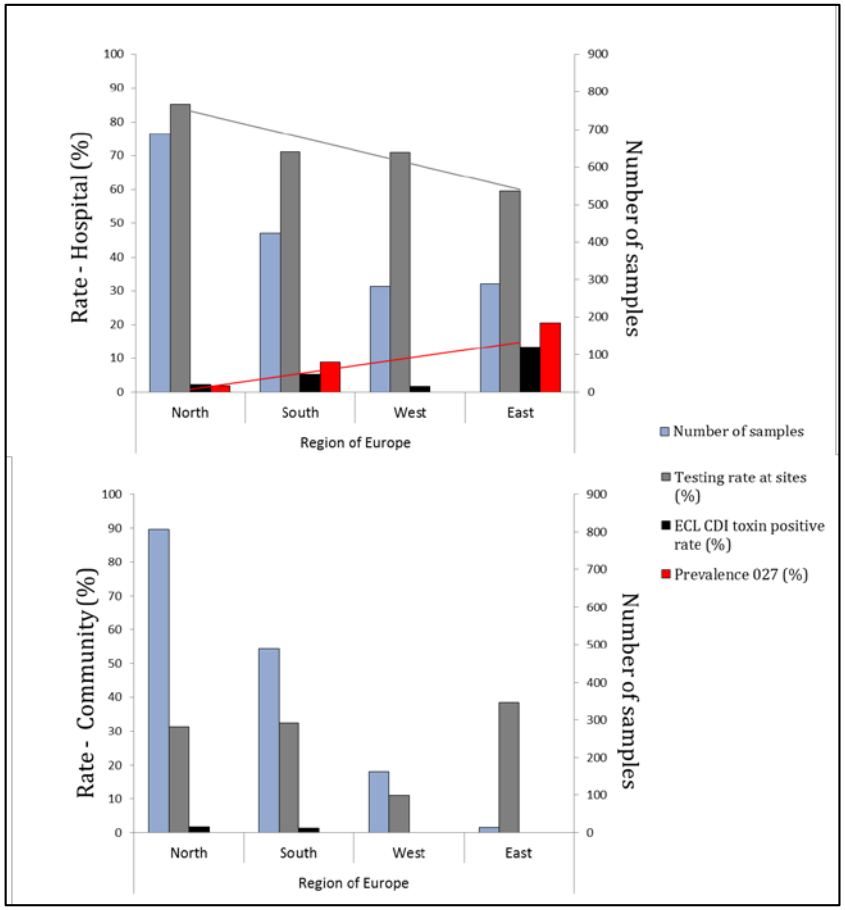


Undiagnosed
- no test at the submitting facility

Misdiagnosed
- False negative - tested but *C. difficile or C. difficile toxins* not detected at submitting facility
- False positive – tested positive for CDI at submitting hospital but negative at ECL

Increased awareness reduces outbreaks

- Comparing the testing rate with the proportion of PCR-ribotype 027 per region of Europe demonstrates that testing rate is inversely related to the proportion of RBT027 strains identified for cases within hospital facilities
  - Highest proportion of PCR-ribotype 027 in Eastern Europe
- This suggests that lack of suspicion and testing leads to;
  - Under-diagnosis
  - Outbreaks of infection
- This pattern is not seen in the community
  - Low level of 027 in the community
  - Need to assess if this pattern is seen with a different PCR ribotype
- This knowledge could also be leveraged to highlight the need for good quality, national level surveillance

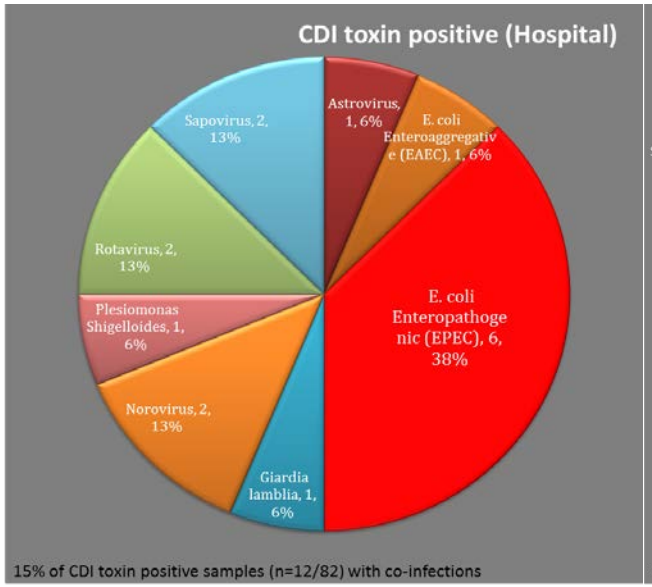


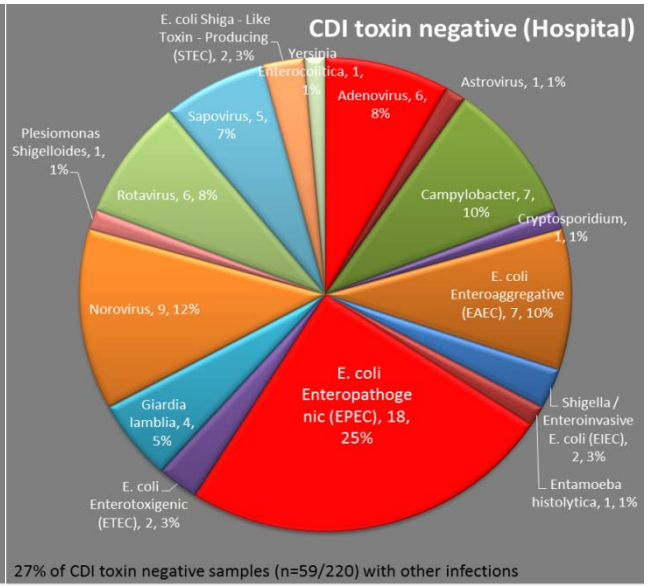
Novel testing methodologies

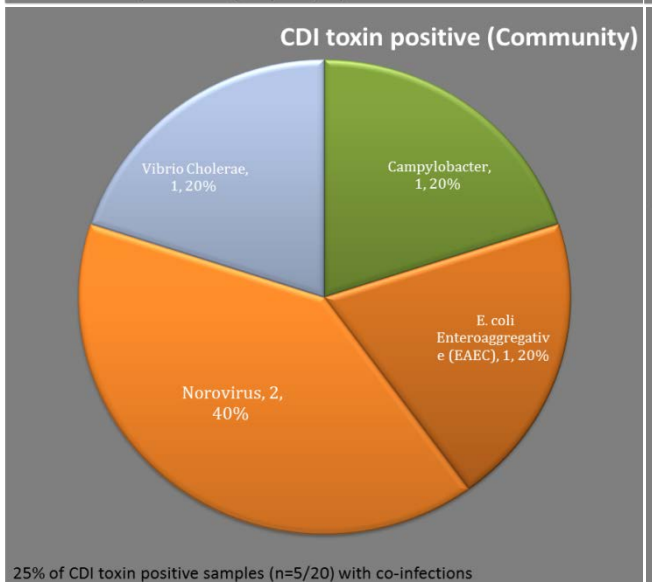
- Samples were also tested using two novel testing methods
  - SIMOA – an ultrasensitive *C. difficile* toxin detection assay
    - Initial data show this assay may be more sensitive than the current gold standard
  - BioFire – a molecular multiplex assay that detects 22 different organisms from the same sample in one assay
    - Useful for looking for;
      - Alternative causes of diarrhoea
      - Co-infections
- There is no current data on using these assays in the community
- Correlation between the results of ultra-sensitive toxin assays and patient data are lacking,

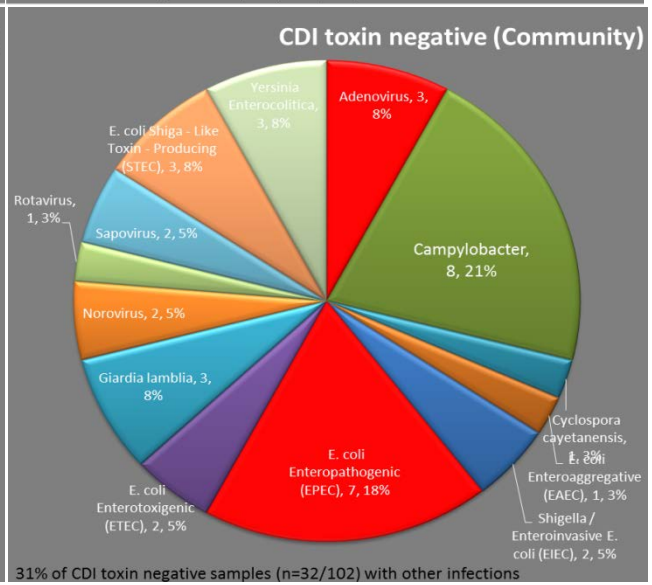
  ➡ This is an important subset to include in the case/control study

Novel testing methodologies







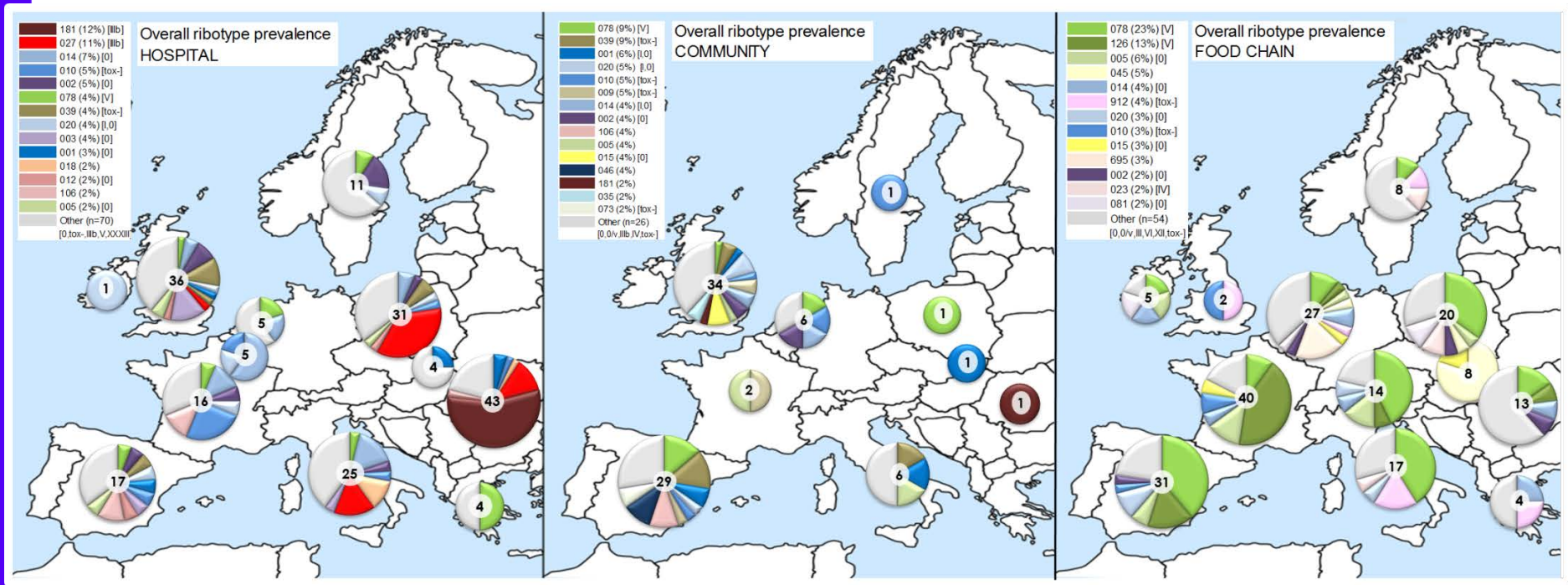


Strain distribution

- Contemporaneous isolates collected from
  - Human diagnostic faecal samples
    - Hospital
    - Community
  - Food chain sources
    - Potatoes
    - Piglets faecal samples

- Typed
  - PCR-ribotyping (Leeds)
  - Toxinotyping (Slovenia)
  - Whole genome sequencing (Consortium pipeline)

Strain distribution



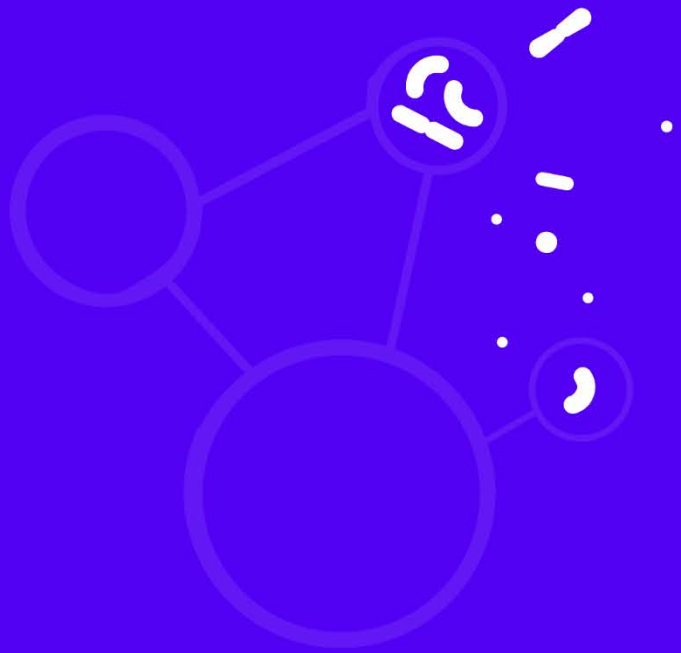
Geographical distribution of *C. difficile* PCR-ribotypes in European countries from hospital and community faecal samples , and from the food chain (food and animal isolates).

Pie charts show the proportion of the most common PCR-ribotypes per country and the number in the centre of pie charts is the number of typed isolates in the country. Toxinotypes identified are shown in brackets.

Strain distribution

- These datasets are unique, as they give;
  - An up-to-date snapshot of the current *C. difficile* epidemiology across Europe, in both the community and hospital settings
  - They show the ‘actual’ circulating strains, not just those isolated from ‘selected’ sample testing, as is the case with most studies
- These data may impact infection prevention guidelines and surveillance guidelines at a national level
- Results feed in to a transmission model in year two

Whats next.....



What's next?

Launched 11th December 2018

- Collect patient data for case/control studies;
- Multiple diagnostic definitions of a case;
  - Case defined as *C. difficile toxin* positive (gold standard method – CCNA) positive
  - Case defined as C. difficile toxin positive (new novel method –SIMOA)
  - Case defined as free toxin negative but positive for a cytotoxigenic strain (by culture or detection of toxin gene)
  - Control defined as negative by all assays
- This enriched case/control study will provide data on the difference in severity of CDI and the risks and outcomes for these different 'diagnostic types'. There are a paucity of data on these differences, particularly with regard to the new technology of the SIMOA assay
- Data then feeds into the transmission model to better understand the interplay between hospital and community cases

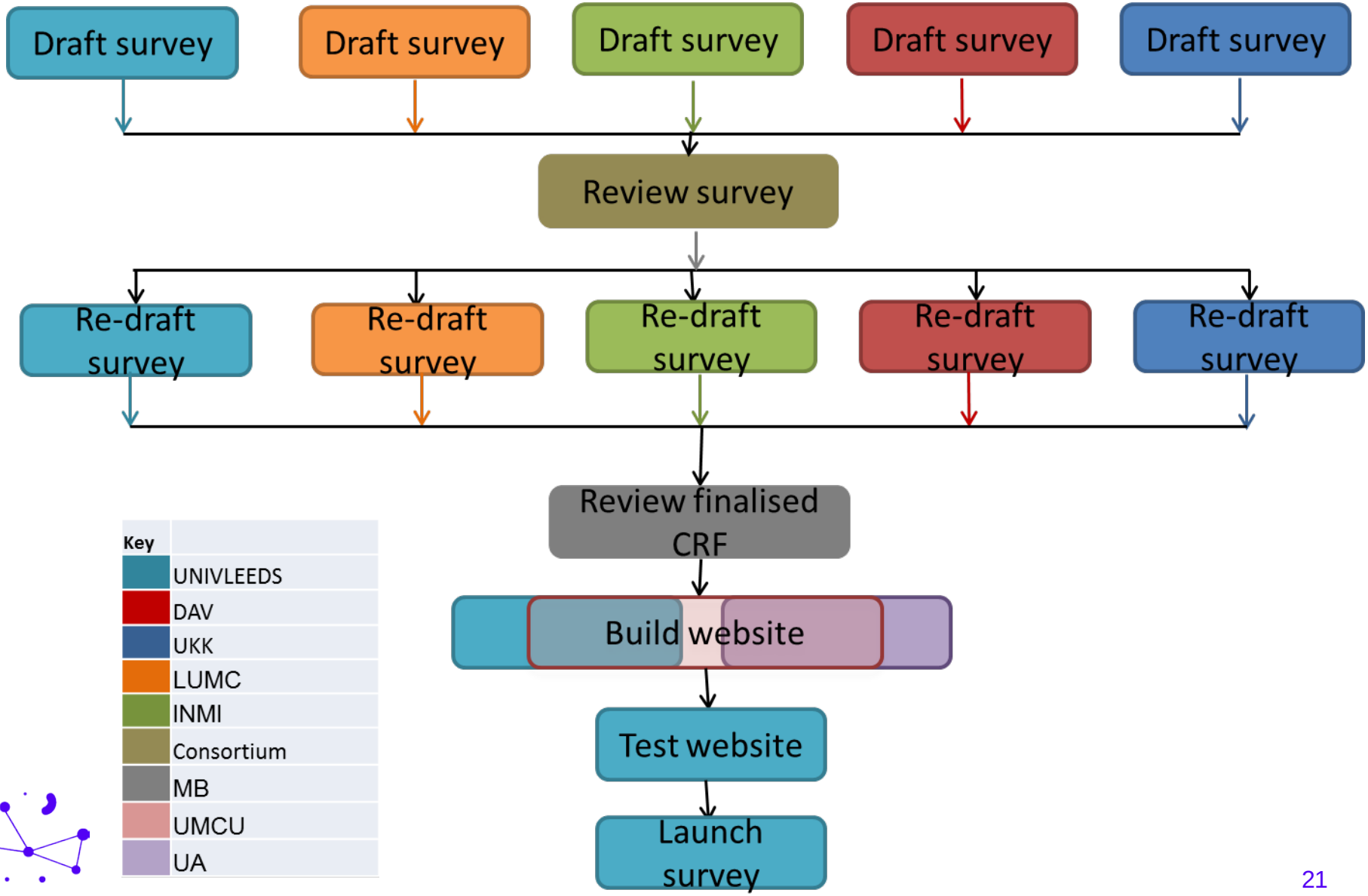
What's next?

Launched
September 2018

- Collect data from hospitals communities via online survey to;
  - Provide an understanding of current guidelines knowledge and compliance
  - Provide evidence for the heterogeneity of testing and how this impacts on case rates and missed diagnoses
  - Provide evidence of current surveillance systems and their effectiveness
  - Provide knowledge on current treatment pathways and differences between community/hospital and between countries

- Align all of the data above to develop a best practice model for *C. difficile* infection prevention, diagnosis, treatment and surveillance

Key collaborations – survey design and build



Acknowledgements

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