Two Weeks in the World | TWIW

Project Portfolio v. 1.1

DTU Food

Version	Last edited	Author	Edits	Contact
1.1	12.03.2020	Sidsel Nag	Major revision, inclusion of new chapters, format change.	sidnag@food.dtu.dk
1.0	16.09.2019	Sidsel Nag		sidnag@food.dtu.dk

Related documents	Availability
Protocol Execution phase – for partners sending isolates v. 1.1	21.02.2020, via email and on the TWIW website
Protocol Execution phase – for partners extracting DNA v. 1.1	21.02.2020, via email and on the TWIW website
Collaboration Agreement	Via email correspondance
Material Transfer Agreement	Via email correspondance

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Executive summary

Two weeks in the world, TWIW, is an academic research project as well as an international collaboration. The current project is the first of it's kind, and was launched in September 2019 as an initiative from the Technical University of Denmark (DTU), The project has since grown in partnerships and been adapted regarding timeframe.

TWIW will shed light on the global distribution of bacterial pathogens, and allow the co-creation of an unprecedented open-access database with clinically relevant samples from around the world.

The TWIW project portfolio is a document for partners and other project stakeholders, with key information regarding project structure, timeline and execution, as well as contact information for the management team and where to find more information regarding TWIW. The project portfolio also contains information regarding the background and justification of the research project, as well as predicted outcome. It is a document formulated in layman's terms, in order to meet the diverse body of professionals who may need to assess the content.

Contact information

The TWIW collaboration is headed by the research group for Genomic Epidemiology (Genepi), at the National Food Institute, Technical University of Denmark (DTU).

For inquiries about TWIW, please contact Project Executive, Sidsel Nag, vie email: **sidnag@food.dtu.dk**

Visit the TWIW website for registration or resources for participants, as well as general information and updates. You may also want to visit the Genepi website.

Physical location:

National Food Institute
Danish Technical University
Kemitorvet, Building 204
2800 Kgs Lyngby
Denmark

01. Project Management

As a newly launched initiative, TWIW project management currently consists of four people. Seeing as TWIW is an academic research project, the team is expected to expand as the project progresses, and students from various university levels will become involved.

02. Project background and justification

Global surveillance of spread and emergence of pathogens, is a key component of our combined activities as a research community in promotion of global health. Global surveillance of diseases and pathogens is being performed at varying scales by a number of institutes and organizations. The output from these efforts vary in scope, quality and reliability due to a number of obstacles encountered by those performing the tasks.

At Genepi, research into the applicability of sewage as a cost-effective and reliable approach to surveillance of antimicrobial resistance (AMR), is ongoing. In the attempt to compare the findings from sewage with findings from clinical samples, in order to assess the applicability of sewage-based AMR surveillance, the obstacles in doing so have become clear. There is a complete lack of an open-access database, with the relevant clinical samples and the necessary metadata, to assess global AMR and pathogen prevalence from clinical cases world-wide.

One of the obvious reasons for the lack of such a database, is lack of data. It is a well-known and acknowledged fact, that data of all sorts, are scarce and sometimes completely lacking, from developing settings. The reasons for this, typically relate back to lacking resources necessary for research and surveillance, as well as being offered unfavorable collaboration agreements, where collaborating institutes simply export the data at a one-time cost, from the country in which it was acquired. Another obstacle is the value that data currently represents. Data is the single most valuable resource coming from research today, and those who have managed to acquire large amounts of data, are also able to use their databases to generate income for their institutions and further research activities.

While it is understandable that research bodies must fund their activities in one way or another, it is important to take note of the increasing acknowledgement within governance, that both infectious diseases and AMR are global phenomena, and require global cooperation in order to be handled properly. If access to databases comes at a cost, those who access the databases will be minimized to those with financial means to do so. Databases with cost-barriers thereby promote inequality in the ability to conduct valuable research and produce research output, which is an important element in financing and developing research institutions. In addition hereto comes the major role played by research institutions in education and capacity building.

02.1 An equity-database through equity research

The long-term goal of TWIW is to produce an open-access database, containing data from clinically relevant samples from around the world. The data includes the species of the (bacterial) pathogen, the sequenced genome of the pathogen as well as minimal metadata applying context to the sample (where and when it was collected). All data generated from TWIW will be uploaded to the European nucleotide Archive (ENA) for open-access no later than 2 years after project termination.

Until the TWIW database is made publicly available, the short-term goal of TWIW is to produce an equity-database of sorts, only restricted by General Data Provision Regulations (GDPR), which need to be adhered to for legal reasons. Creating the intended database requires massive efforts, not least from those who collect the bacterial isolates that make up the database. In lack of funding for compensation of wages and labor put toward their participation in TWIW, partners are offered mutually beneficial partnerships on the TWIW project. This includes shared ownership of and immediate access to the data generated from the isolates they have acquired for TWIW, and invitation to lead study initiatives based not only on the data they have provided (this has been specified under Chapter 11. Partner-lead study initiatives). Genepi aims to supply material and protocols necessary for participation according to the format chosen by partners. In addition, Genepi covers all costs of shipments, sample handling and processing as well as down-stream analyses performed at DTU. Any partners with resources that could be put towards co-financing these efforts are most welcome to do so. Lastly, partners are of course offered involvement in and co-authorship of any research-output involving their efforts (including data and isolate acquisition).

With the above framework in place, the ambition is to co-create a comprehensive database with clinically relevant samples from patients suffering from bacterial infections, all around the world. Assuming that we succeed in our ambitions, the TWIW collaboration and database will serve as a foundation for a number of studies, some of which are listed under Chapter 10. Predicted outcome.

Should funding be available, Genepi aims to repeat the TWIW project in 2021.

03. Project overview

Genepi responsibility

Partner responsibility

Invitation phase
Identify and invite potential partners and networks relevant for the project

1

2

Registration phase
Interested partners register for participation

Preparation phase
Send sampling material and relevant protocols to partners according to participation format.

3

4

Execution phase
Select samples, collect metadata, isolate bacteria and/or extract DNA. Transfer samples and data.

Handling and processing phase
Log, regrow and freeze samples. Extract DNA, perform sequencing. Quality assessment.

5

6

Analysis phase
Species identification, AMR and VIR gene identification. Context and prevalence studies. Phylogeny.

Dissemination phase
Manuscripts and abstracts, reporting to partners and stakeholders

7

8

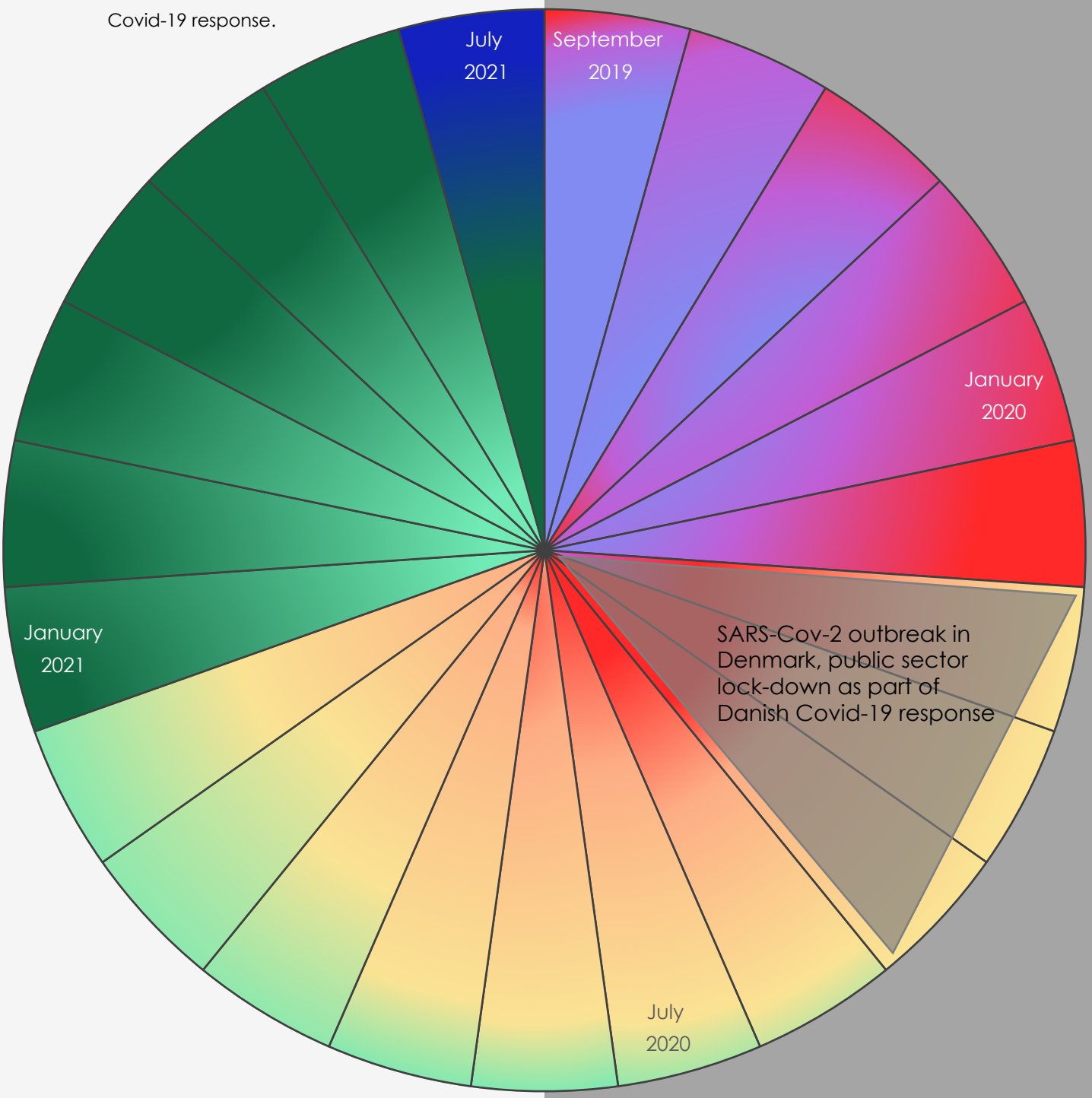
Closing phase
Final project assessment incl. lessons learnt.

Timeline colour-code

03.1 Project timeline

The chart illustrates the distribution of the eight project phases across an expected project timeline of 24 months. This timeline may be subject to change, and has been further adjusted as a consequence of the Danish Covid-19 response.

Project phase colour-code

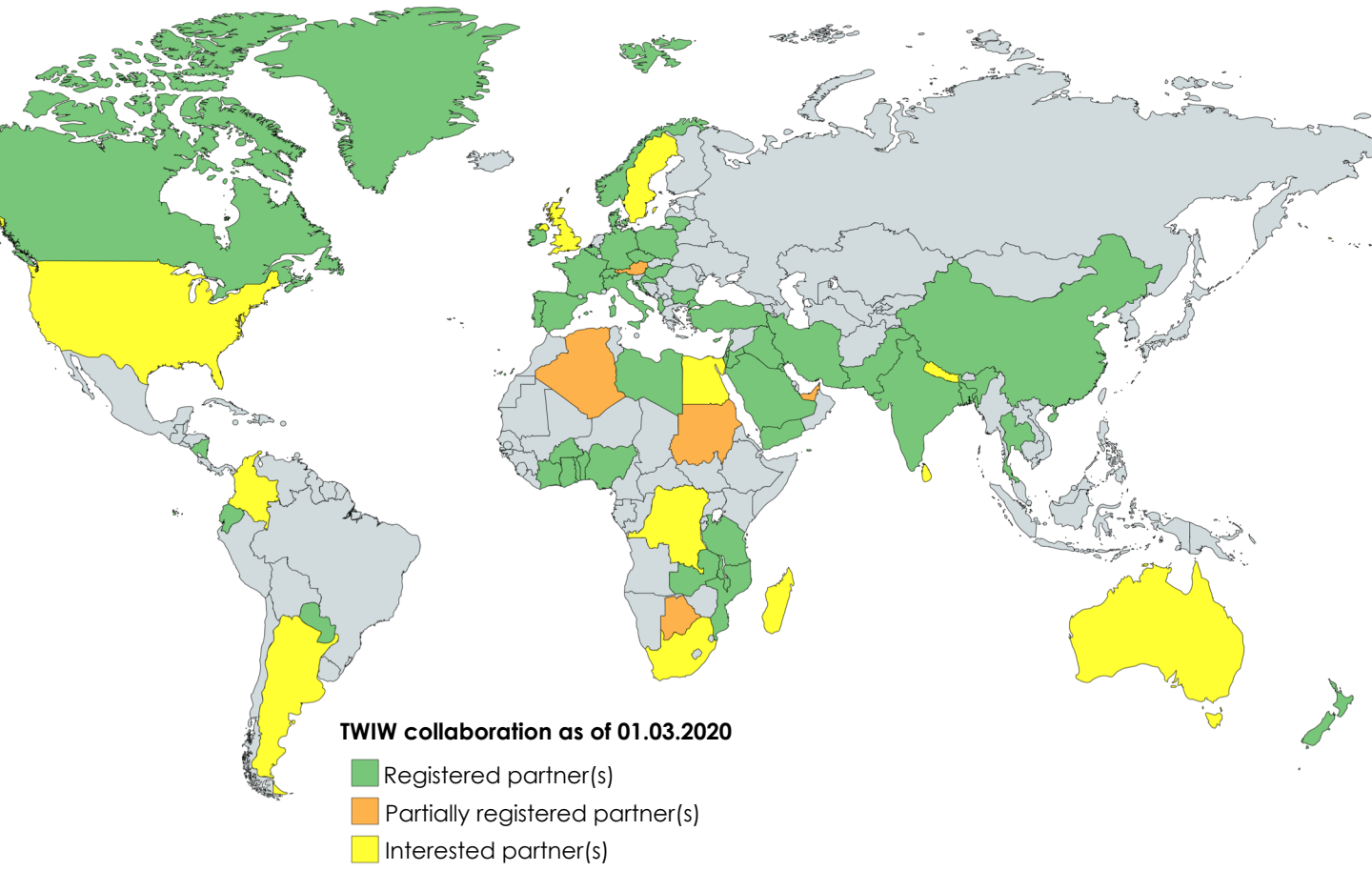


04. Community, transparency and resources

The TWIW website will be used for updates of relevance to the entire TWIW-community, as long as these are not confidential of nature. Furthermore, any resources (protocols, video guides, safety documents, etc) produced for the TWIW collaboration, or of relevance to the participation of partners, will be accessible on the website. Partners will also receive regular TWIW updates via email.

We seek to promote transparency in every aspect of the TWIW-collaboration, and balance doing so with relevant GDPR regulations.

A map of countries participating in TWIW will be visible on the website, but collaborating institutions will only be listed if permission is given by the entity.



05. Ethics, GDPR and legal aspects

TWIW is a project collecting bacterial isolates from patient samples, as well as minimal metadata related to the samples. This aspect of the project demands of us, that we comply with national and international guidelines regarding ethics, including GDPR.

For this purpose, in addition to having a Material Transfer Agreement (MTA) in place with partners, we also have a Collaboration Agreement, which goes hand in hand with the MTA. The Collaboration Agreement is a document defining the legal aspects of our collaboration with the individual partner. Amongst these aspects lies the placement of responsibility of adhering to the national laws governing patient rights as well as patient's potential ownership of their own data. These laws are defined by the country in which the patient resides at the time of being a patient, and adherence hereto therefore needs to be the responsibility of the partner. Details can be found in the Collaboration Agreement.

Amongst the material sent to partners for sampling bacterial isolates for the study, are sample labels, which are generated by Genepi. These labels follow a TWIW-specific code system, and partners will use these labels to place on the samples and the data sheets with relating metadata. Once the samples arrive in Denmark, the samples will be given a working number, for laboratory processing. This is done to ensure that partners do not use patient-tracible identifiers to name samples for TWIW, and in order to double-blind the sample-identifiers.

06. Formats for partner participation - execution phase

TWIW partners can participate in three formats:

Format 1: collection of bacterial isolates and minimal metadata

→ Transfer of isolates and minimal metadata

Format 2: collection of bacterial isolates and minimal metadata with in-house DNA extraction

→ Transfer of extracted DNA and minimal metadata

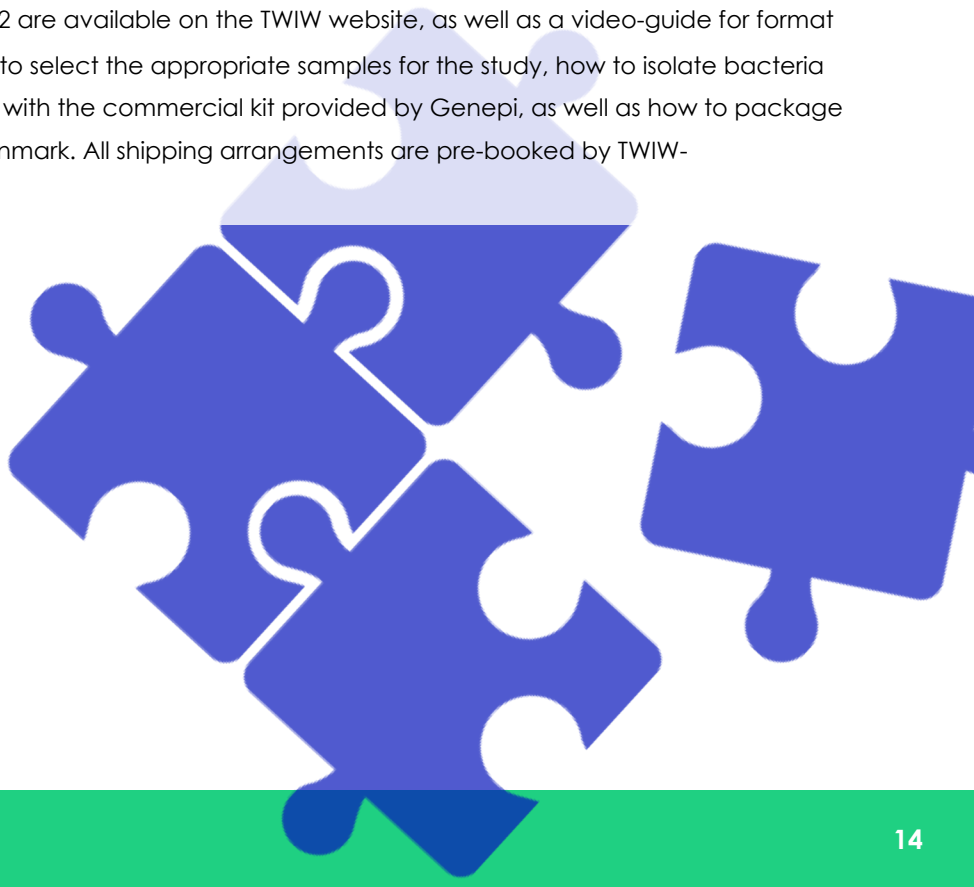
Format 3: collection of bacterial isolates and minimal metadata with in-house DNA extraction and next-generation sequencing

→ Transfer of raw sequencing data and minimal metadata

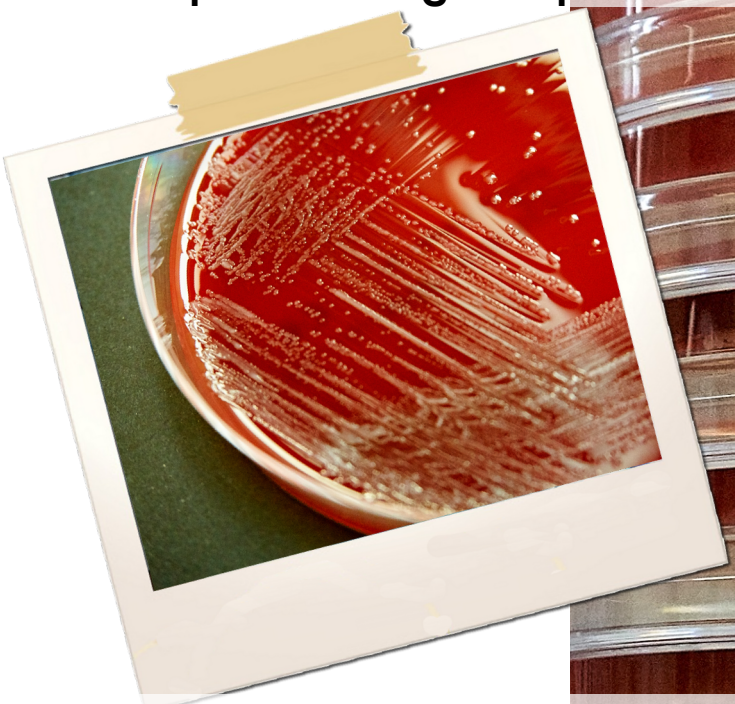
Mandatory minimal metadata consists of:

- Date or week of sampling from patient
- Source of patient sample (blood, urine, nasal swab, etc)
- Date or week of isolation from laboratory
- Species identified

Protocols for formats 1 and 2 are available on the TWIW website, as well as a video-guide for format 1. The protocols cover how to select the appropriate samples for the study, how to isolate bacteria and/or how to extract DNA with the commercial kit provided by Genepi, as well as how to package and ship the material to Denmark. All shipping arrangements are pre-booked by TWIW-management.



07. Sample handling and processing



Project executive will be notified when packages are received at DTU.

Samples received will be handled according to their nature (isolates or DNA).

Isolates:

Isolates received will be kept at 4°C in the loading bay until picked up by Genepi staff. Once picked up, isolates will be regrown and DNA will be extracted immediately from anaerobic, microaerophilic and other fastidious species. Other species will either be frozen for later processing, or DNA will be extracted, depending on the overall capacity in the laboratory.

DNA:

DNA is stored at room temperature in the loading bay until picked up. Once picked up, DNA will be stored at 4°C in the laboratory. Concentrations will be assessed, and samples will be included for library preparation with the DNA extracted by Genepi.

Library preparation will be performed according to Illumina's Nextera XT library preparation protocol, and sequencing will be performed on Illumina technology. Select samples may be sequenced on Minion technology.

Raw sequencing data transferred by partners will be incorporated in down-stream analyses, including raw-read quality assessment, species identification and identification of AMR and VIR genes.

08. Data sharing and accessibility

Once sequencing data is available for samples provided by a partner, these will immediately be available for download through a cloud-based platform.

The complete TWIW database will be a MySQL database hosted on Computerome, the National Life Science Supercomputing Center. All parameters will be stored in the database and access will be permission-based (as is all Computerome access).

Partners can be granted access to more than their own data, if permissions are granted by the data owners and GDPR guidelines are adhered to.

09. Predicted outcome

Feasibility concept note

Is it possible to overcome the practical, logistical, ethical and financial constraints in acquiring clinically relevant samples from around the world? Can we produce a reliable database from the outcome? And what is involved in doing so?

Diversity in diagnostics

How do the diagnostic units involved in TWIW differ? What are the differences in populations represented and resources at their disposition? How does this reflect on our understanding of burden of disease?

"Real" burden of disease and QA

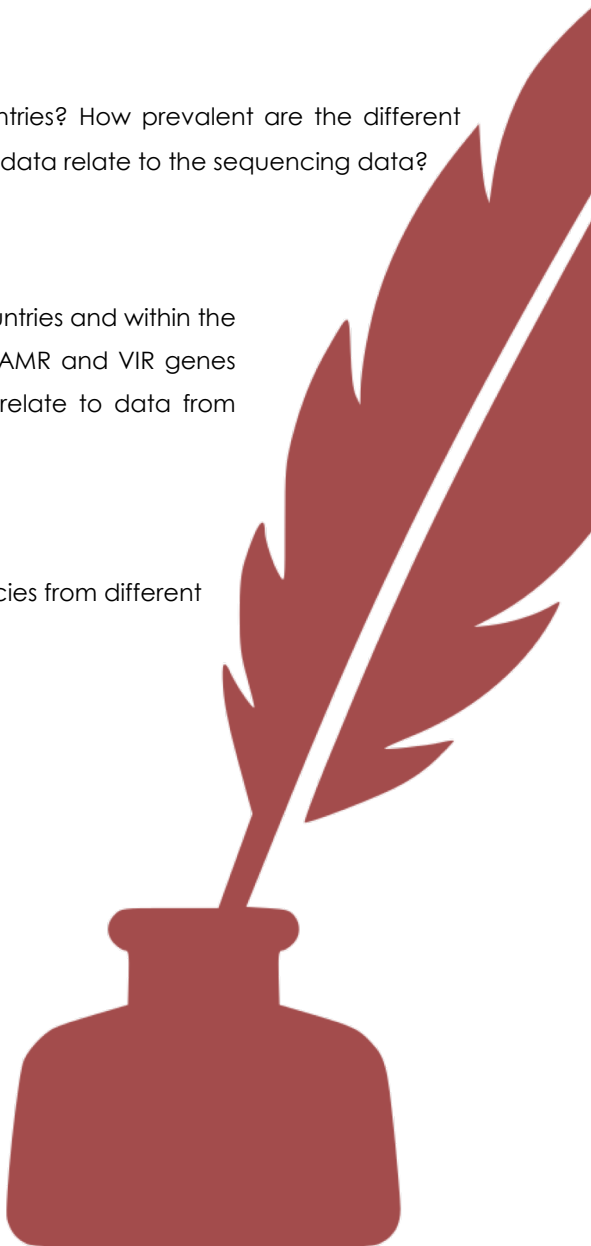
Which bacterial pathogens are found in the different countries? How prevalent are the different pathogens in different settings? And how do the diagnostics data relate to the sequencing data?

Antimicrobial resistance and virulence

Which AMR and VIR genes are found within the different countries and within the differen pathogens? How does the abundance of various AMR and VIR genes distribute across global regions? And how does this data relate to data from sewage?

Phylogeny studies

What is the phylogenetic relationship between identical species from different settings?



10. Partner-lead study initiatives

In order to maximise the use of TWIW-generated data and the research output from TWIW, we invite partners to lead study initiatives not listed as part of the expected output from TWIW (which will default be lead by Genepi, with involvement of all partners).

Partners interested in leading study initiatives will send their proposal to Sidsel Nag (TWIW project executive), including the following information:

- Objective of the study
- Necessary data access for performing the study
- Partner's capacity to perform the study (professional resources as well as analytical resources)
- Expected timeframe for performing the study

Partners requiring access to data provided by other partners, will not be given access until permission is granted by all data owners (Genepi + sample provider). All partner-lead study initiatives must be carried out with involvement of all partners providing data for the study, to the extent that these wish to be involved.

We do not expect noteworthy overlap in the demand to lead specific studies, but if such overlap should occur, discussions as to who will lead the study will be held with all interested parties, and Genepi retains the right as project owner to make a final decision. Please note that, as mentioned above, access to data provided by other partners, cannot be granted without permission from these partners, until all data is uploaded to ENA, and made publicly available no later than 2 years after project closing.

Decisions regarding partner-lead study initiatives, will not be made until onset of the analysis phase, as there cannot be made any guarantee's regarding the data output from TWIW until then. All partner-lead study initiatives will be published at the time of initiation, on the TWIW website, in order to promote full transparency for partners.

11. Project assessments and refinement

If funding is available, TWIW will be repeated in 2021. It is therefore a priority to assess the project, both with regards to management and execution, as well as outcome and future perspectives. Partners will be involved in this assessment, to the extent that they are able to commit.

Ad hoc feed back of all sorts is entirely welcome and appreciated.