Vaccinating
Elderly for
Healthy Ageing

WP2: Understanding and improving immunity to infections and vaccination in the aging population

5.1.2e

The VITAL project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 806776.
The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Aim and ambition

overall objective

This WP will provide a better understanding/characterisation of the immune response of aging adults after vaccination, delineate important (internal) factors predictive of vaccine response, how that could be affected by external factors and will provide leads to improve immune responsiveness in the elderly by vaccinating at the pre-elderly stage.

This fits with the overall project ambition to

- improve efficacy of vaccines in elderly
  and better protect the growing ageing population against infectious diseases.
  by modulation of specific vaccine immune responses
- Work towards a more targeted immunization program for the elderly
  that will contribute to healthy aging.
  Through identification of specific groups for vaccination

Perform clinical vaccination study

VITAL Vaccinating Elderly for Healthy Ageing

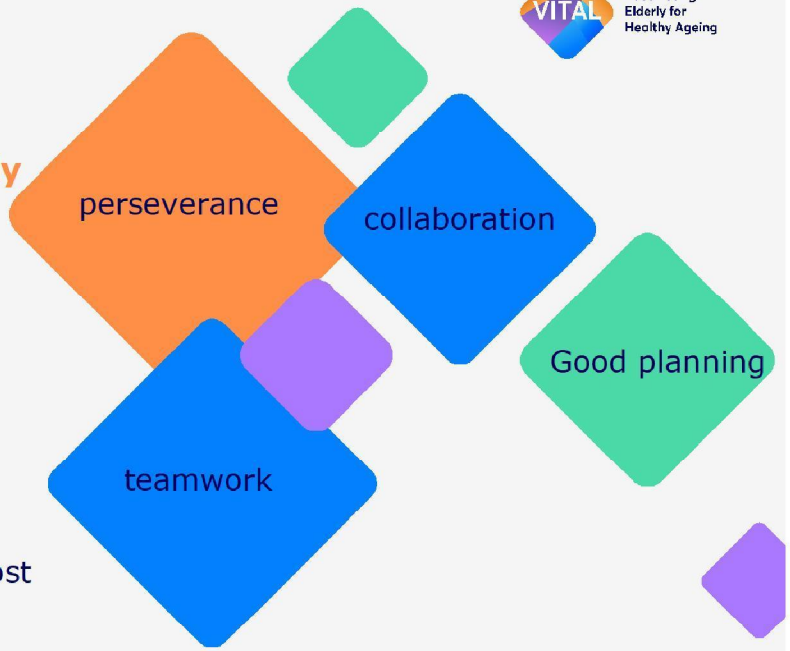
To design optimal future vaccination strategies for ageing adults and understand the mechanisms of immunosenescence

Key Objectives Year1

Vaccinating Elderly for Healthy Ageing

perform prospective clinical vaccine study

- Study Protocol clinical vaccines study
- Ethical clearance clinical vaccine study
- Recruitment participants
- First visits and initiation vaccination
- Complete influenza follow-up until 1 month post vaccination
- Division of tasks between partners and timeline primary assays for vaccination response



The design of the clinical trial:

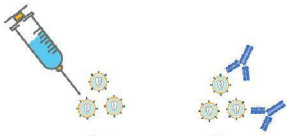
VITAL Vaccinating Elderly for Healthy Ageing

Individuals from 3 different age groups

- Older adults 65+
- Middle-aged adults 50-65
- Young Adults 25-50

People who had the influenza vaccination of the last year and never had the pneumococcal vaccine before are recruited for the study

Quadrivalent inactivated influenza vaccine (QIV) in October 2019



(Booster)

Pneumococcal conjugate vaccine (PCV13) in March 2020

(Primary)

The design of the clinical trial: Sample collection

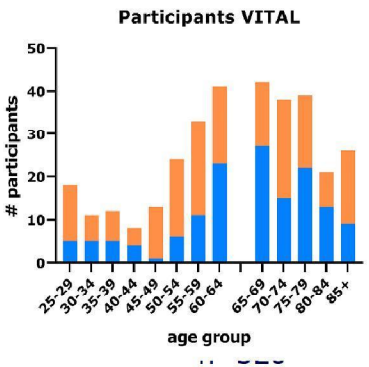
Vaccinating Elderly for Healthy Ageing

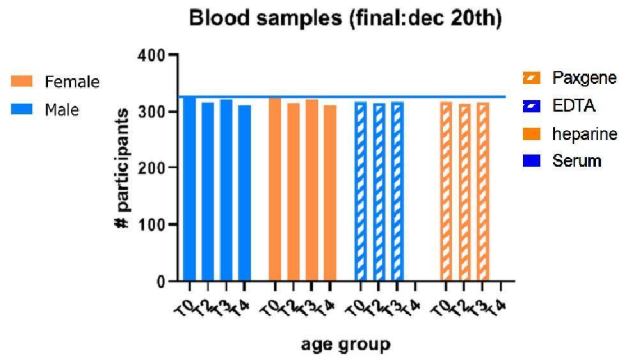
Time points (Influenza part)

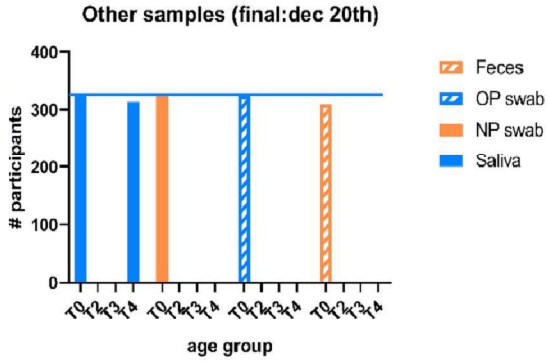
- ❑ T0 pre-vaccination → baseline parameters
- ❑ T1 influenza vaccination
- ❑ T2 1 or 2 days post-vaccination → innate immune response
- ❑ T3 7 days post-vaccination → adaptive immune response
- ❑ T4 28 days post-vaccination → antibody and memory adaptive response

Achievements year 1: Influenza vaccination

Vaccinating Elderly for Healthy Ageing







>84,000 Vials of serum

Total blood in ~16 adults

>8000 PBMC vials

~90 boxes in the freezer

954 Trucounts

>80 hours at Flowcytometer

Beneficiary contributions and integration within the action

Vaccinating Elderly for Healthy Ageing

Partners	Period 1 WP2 contributions
UMCU	In process of hiring bio-informatician for integrated data analysis, assisting in execution clinical trial Design of frailty assessment
RIVM	Lead in the design of the clinical trial, Execution clinical trial, questionnaire data collection, biological sample preparation and storage, realtime analyses of immune cells. Discussion on choice for assays, time points sample collections and timelines for lab and data analysis. Influenza vaccine supply, WP2 lead: coordinating and overseeing activities
UMCG	Design of assays and timelines for measurements, Design of frailty assessment
INSERM	Design of assays and timelines for measurements
UIBK	Design of assays and timelines for measurements
UCL	Advisor
ICL	Advisor
CNRS	Advisor
UNIFE	Design of assays and timelines for measurements
UJM	Design of assays and timelines for measurements
GSK	Co-leadership of WP2; Review and input in clinical protocol and ICF, active participation to WP2, setting up of HAI testing incl. logistics, budget and contractual aspects;
PFZ	Arrangement of contract to supply PCV13 vaccine for the clinical trial, Design of the trial
SP	Providing materials for RNA transcriptomic analyses Providing Influenza antigens for T and B cell measurements Design of assays and timelines for measurements
MSD	Design of assays and timelines for measurements
JVP	Design of clinical trial
BMX	Providing materials for RNA transcriptomic analyses, Design of assays and timelines for measurements

WP management

* *During the writing of the protocol several TCs were held to discuss specifics of the trial*
* *A F2F meeting was held to discuss the specific assays (who to perform, what assays and when)*
* *For the primary outcomes, assays have been chosen and specific timelines have been set.*
* *During the GA adjustments were made in the time lines where necessary*

- *Issues were discussed, problems were solved by interaction with all partners. Despite the large number of participants we work together to make sure we end up with an impactful result.*
- *Currently, regular TCs and F2F meetings are planned to keep everyone informed on trial progress and results.*

Current relevance of the objectives

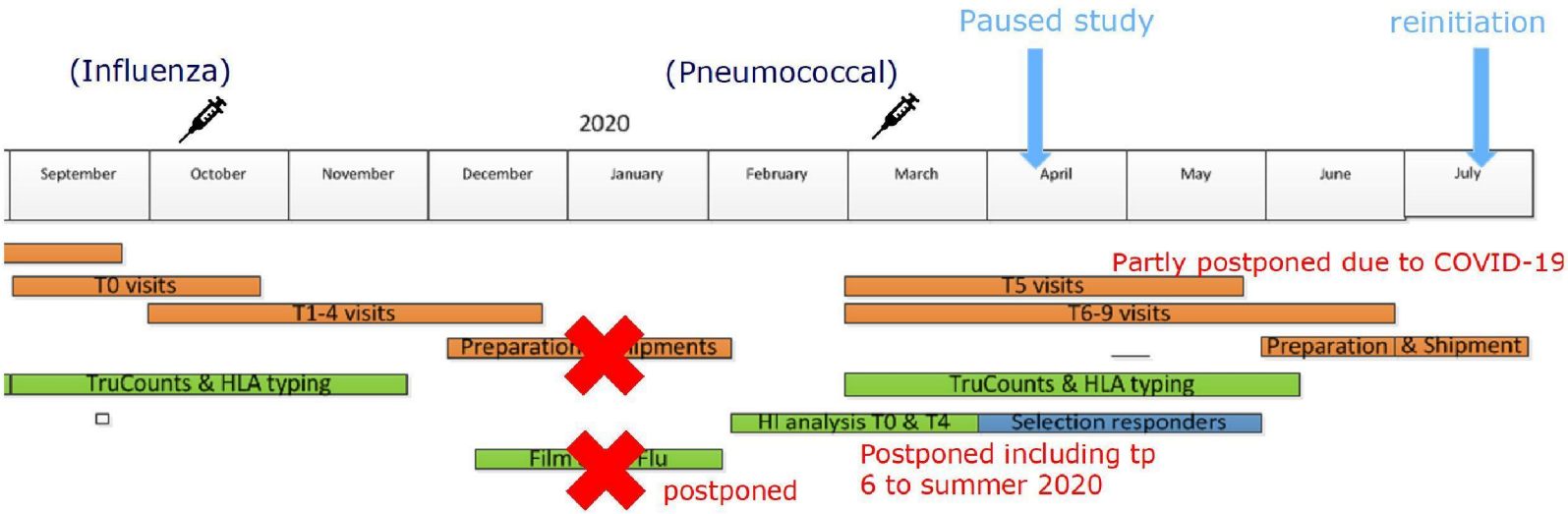
* *Especially now with the new COVID-19 outbreak which affects mostly older adults, our objectives are highly relevant.*

  We need to understand why elderly respond worse to infections and vaccinations and have vaccination strategies available to protect the most vulnerable people.

* *Given the broad aspects under study for two still highly important infectious dieases and the potential to extrapolate the results to other infectious diseases in the future, we expect to:*
  - identify novel biomarkers and immune signatures or clinical phenotypes associated with vaccination response

  This will lead to identification of risk groups and targeted vaccination programmes.

Timeline: COVID impact



Progress clinical study phase 2 (PCV13 vaccination)

Status:

M0-D1/2- D7-M1 samples in freezer

Fingerprick samples collected in July in freezer:

HI assays performed

Looking Ahead – from Mid-term to Project End

- Finalizing the clinical study (Sept 2021):
  - 6M follow-up PCV13 vaccination
  - 12M follow-up/end of study

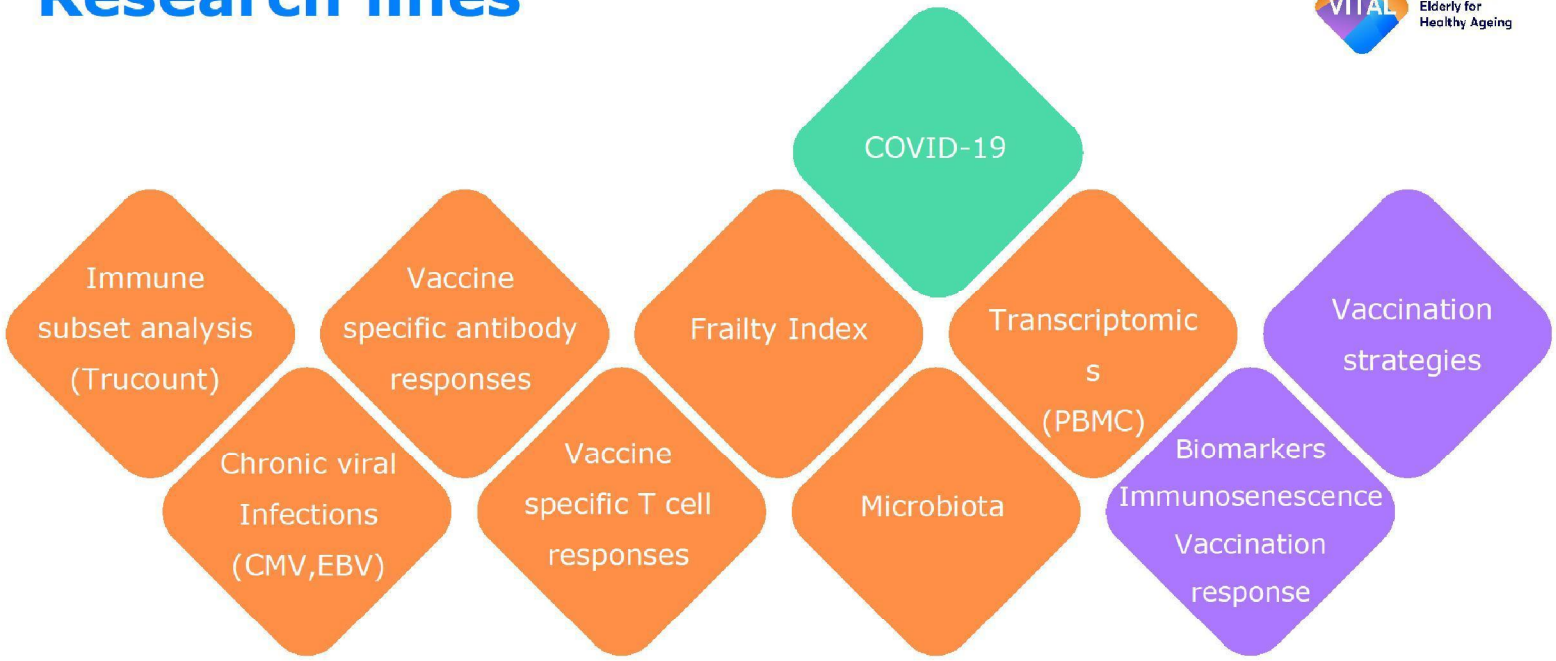
- Planning/execution of primary assays:
  - pneumococcal antibodies
  - Flu-specific T cells (T cells)
  - mucosal immune responses

- Primary Analyses and integration of data to define responder profiles

- Selection of participants for indepth studies

> Working towards novel biomarkers and immune signatures

Research lines



COVID-19 related research

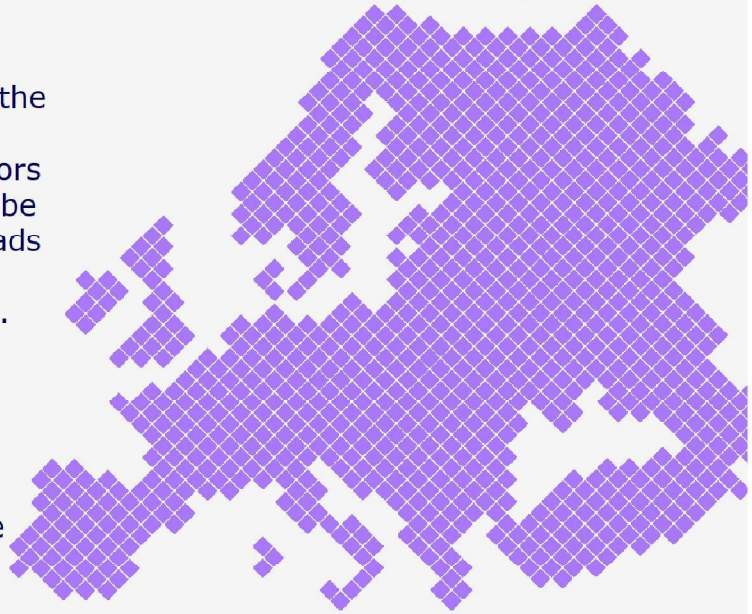
Vaccinating Elderly for Healthy Ageing

Questions (necessary vs optional)	approach
Effect of COVID-19 infections on study outcome	Check participants for ILI-sympotoms during follow up (continuous) Questionaire on proven COVID-19 infection (July 2020) Perform COVID-19 serology - tp July 2020 - tp fall 2020/spring 2021
COVID-19 specific immune response analyses in COVID-19 exposed individuals	Identify COVID-19 exposed participants Analyse functional antibody induction(neutralizing antibodies) Analyse induced COVID-19 specific T cell memory immunity

Impact & dissemination

Vaccinating Elderly for Healthy Ageing

- This WP will provide a better understanding of the immune response of aging adults after vaccination, delineate important (internal) factors predictive of vaccine response, how that could be affected by external factors and will provide leads to **improve immune responsiveness in the elderly** by vaccinating at the pre-elderly stage.



Specific features:

- Recommendations on vaccinating aging adults:
- New knowledge on vaccination in aging adults
- Deeper understanding of the immune-response and vaccinology in aging adults
- In depth analyses of aging adult vaccines
- Prevaccination (bio) markers for decreased vaccine responsiveness
- Exploration of new data and analysis methods

On track
On track, at risk
Off track

VITAL WP2
Summary slide

Vaccinating Elderly for Healthy Ageing

fullfilled Milestones or Deliverables

Milestone/Deliverable	DoW Date	Actual Date	Status
D2.1 (protocol ready)	M_3	15/4/2019	
D2.2 (METC approval)	M_6	3/7/2019	
D6.1-6.5 (ethical issues)	M0-7		
D2.3	M_9	7/10/2019	

Current Issues & Risks

- COVID-19 slows down the clinical study. Mitigation plans in place, expected delay at least 6M

Accomplishments / Highlights

- Study Protocol.
- Time lines primary assays
- Consensus on assays
- Antigens needed for assays
- Ethical clearance
- Initiation of recruitment
- Labprotocols and personnel for sample collection
- Initiation of T0 visits for 326 participants
- Finalization M1 visits after flu vaccination
- Initiation and M1 follow up PCV13 vaccination

Actions for next period

- Plan final visits PCV13 part
- Prepare shipments for analyses
- Start analyzing the first data

Thank you for your attention

Vaccinating Elderly for Healthy Ageing

For more information visit our website https://vital-imi.eu/

Vaccinating
Elderly for
Healthy Ageing

Work Package 2 Back –Up slides
VITAL Mid-term Review Meeting

5.1.2e

The VITAL project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 806776.
The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

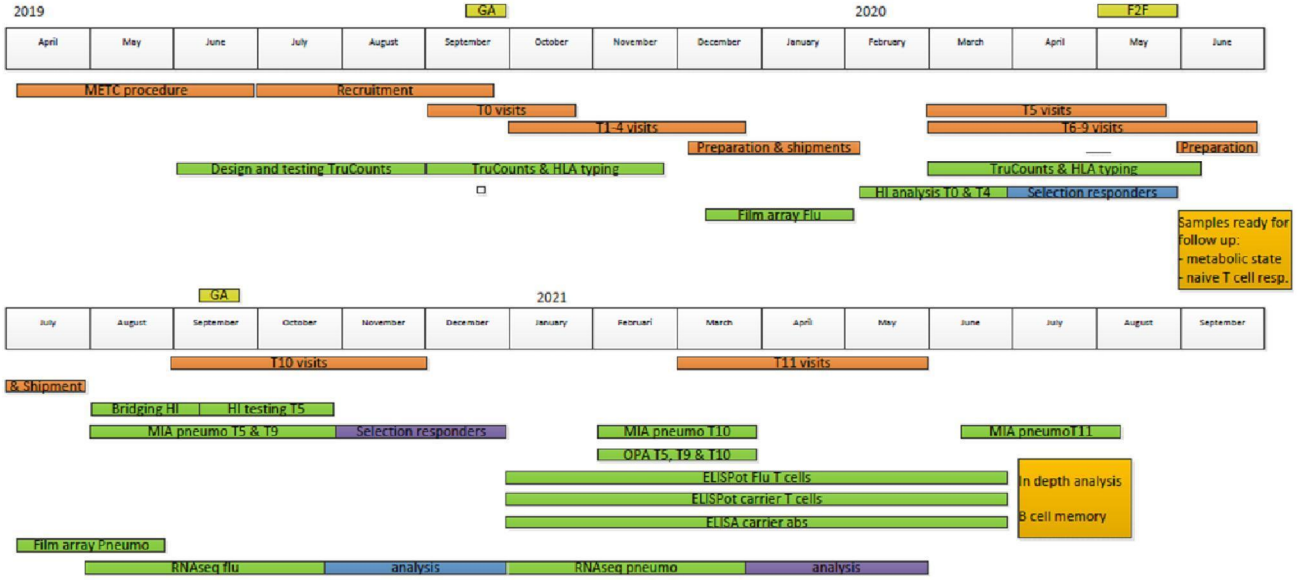
WPx Milestone/Deliverable Progress

Back-up slide

Milestone/ Deliverable	Due Date	Completed (Y/N/Partial)	Level of Dissemination: *PU = Public, fully open, eg, web; CO = Confidential, restricted under conditions set out in Model Grant Agreement; CI = Classified, information as referred to in Commission Decision 2001/844/EC*	Reason for Delay	Key Action to Get Back on Track	New Estimated Completion Date	Impact to WP, Other WPs, and Overall Project

Vaccinating Elderly for Healthy Ageing

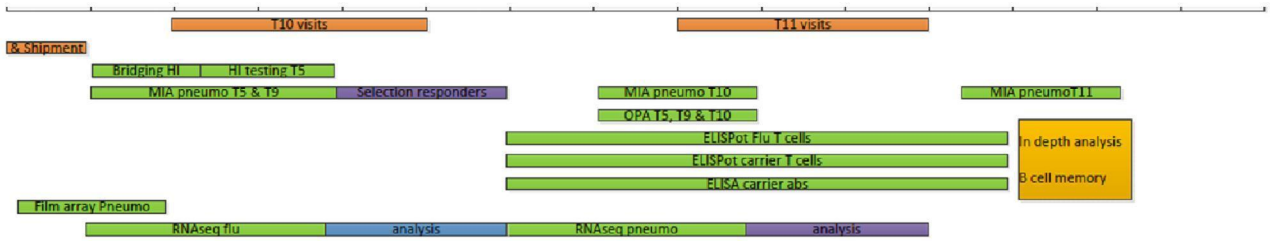
Action plan next year(s)



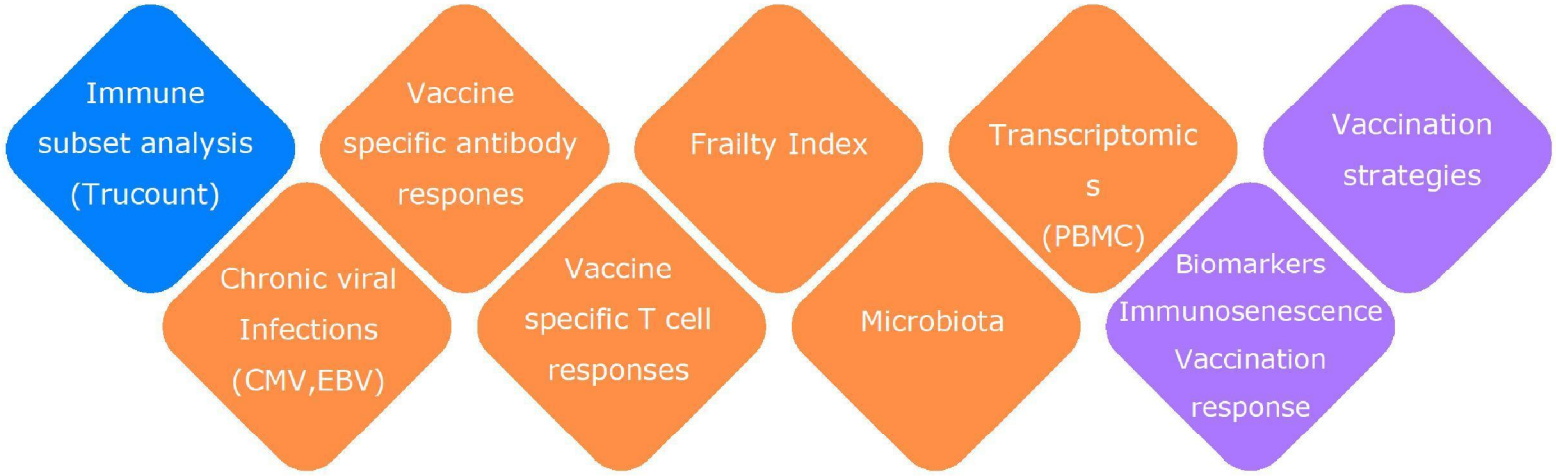
Update progress analyses phase 1

Vaccinating Elderly for Healthy Ageing

- Flu-specific antibodies in serum



Research lines



Trucount panel: *main cell subsets and activation markers*

FITC (BB515)	**CD25**
PerCP Cy5.5	**CD45**
APC	**CD127**
APC	**CD14**
AF700 (APC-R700)	**CD56**
AF700 (APC-R700)	**CXCR5**
APC-Cy7 (APC-H7)	**HLA-DR**
BV421	**CD8**
BV421	**IgD**
BV510 (BV480)	**CD38**
BV605	**CD3**
BV650	**CD86**
BV711	**CD27**
BV786	**CD45RO**
PE	**CD95**
PE-CF594	**CCR7**
PE-Cy7	**CD16**
BUV395	**CD19**
BUV737	**CD4**

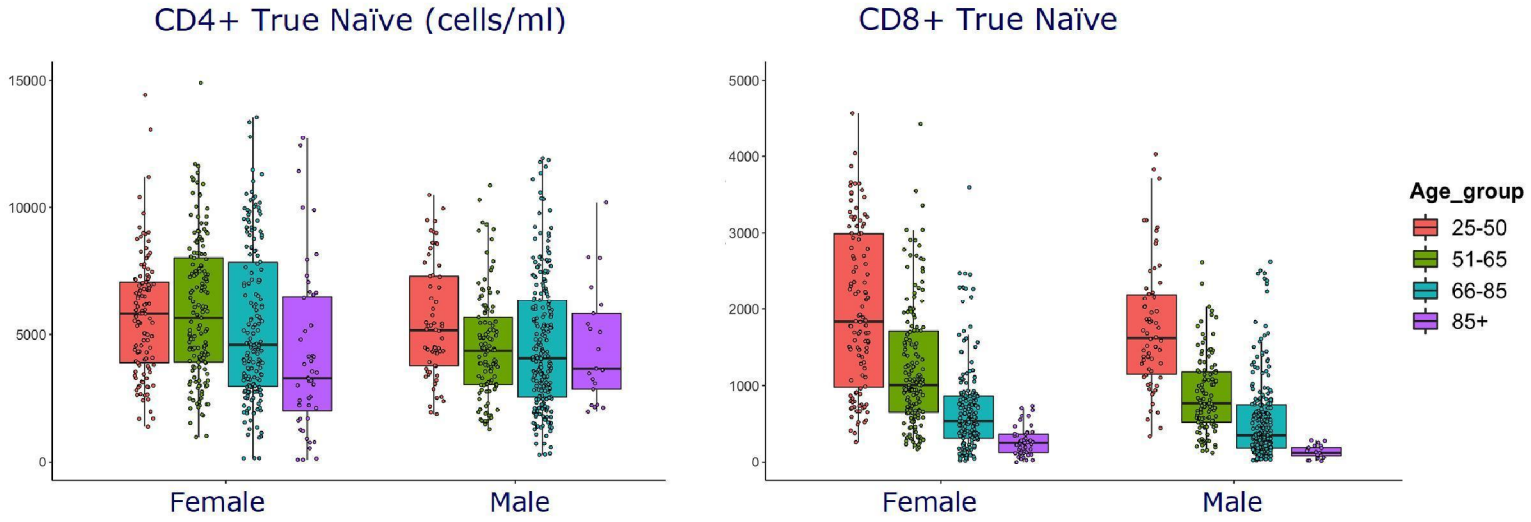
16 colors, 19 markers

Counting beads

- ❑ Granulocytes
- ❑ NK cells
  - ❑ CD56bright, CD56dim
- ❑ NKT cells
- ❑ Monocytes
  - ❑ Classical, intermediate and non-classical
- ❑ T cells
  - ❑ CD4, CD8
  - ❑ Treg, Tfh, Tscm, Tcm, Tem, Teff
- ❑ B cells
  - ❑ Naïve, plasmablast, memory

True Naïve CD4+ & CD8+ T cell numbers decline with advancing age

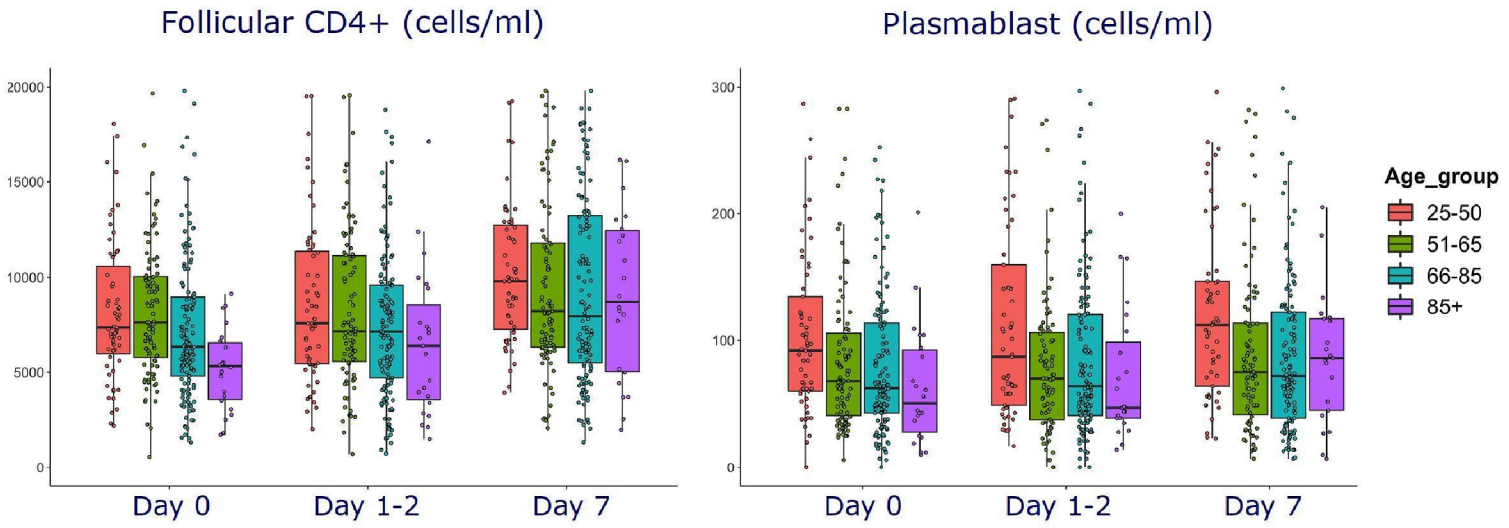
Vaccinating Elderly for Healthy Ageing



True naïve: CD45RO- CCR7+ CD27+ CD127+ CD95-

Plasma cell and follicular CD4+ T cell numbers increase after vaccination

Vaccinating Elderly for Healthy Ageing



/ / Page number 26

Plasmablast: CD19+ CD27+ CD38+ Follicular CD4+: CXCR5+ CD4+

Resource planning and use

- As main activities in the first year were centered around the execution of the clinical trial mainly resources were used from the RIVM budget.
- Recruitment, planning, blood sampling and storage were way more elaborate then anticipated, so a large part (50%) of the budget was already spend.
- By aligning with regular activities we anticipate to spread costs for the next year.

Lessons Learned – Project Initiation to January 2020

Vaccinating Elderly for Healthy Ageing

- Communication is of utmost importance
- Perseverance is important to reach goals (f.e. recruitment of participants)
- Really exceptional wide variety of experts in the consortium
- Willingness to work together is impressive
- This project and its goals are of top priotity for establishing an effective vaccination strategy to protect elderly from infectious diseases
- Collaboration with other IMI projects could help in harmonization of assays (Flucop)

Cross WP interactions

- *Frailty assessment exchange for bridging the WP1 prospective study with the clinical vaccine study*
- *Gathering data on Health networks around the older adults in the clinical vaccine trial for WP4*
- Discussing on frailty and how to include the ageing aspect in WP3
- First paper finalized introducing the project with all Wpleads

WP2 Issues/Risks/Challenges/

Current Issues/Risks/Challenges	Proposed risk-mitigation measures
▪ Location of vaccination site ▪ slower recruitment rate due to summer period and previous vaccination requirement ▪ Lot of work for current planning and recruitment team • Low recruitment of young age group, especially males aged 40-50	All foreseen and unforseeen issues and challenges were solved In the end 326 individuals were included with enough power for the primary objectives and plenty meaterial for indepth studies
Novel risks:	
• Location of vaccination side • COVID-19: - drop out of participants - personnel for blood draws/lab - visits to elderly - shipments of material and subsequent analyses	Solved Current participants in follow-up after vaccination will be followed. New vaccinations will be postponed. Plan B will be initiated when restart is not possible in april/may adjust assay planning

Acknowledgements

The clinical study team:

5.1.2e
5.1.2e
5.1.2e
5.1.2e
5.1.2e
5.1.2e
5.1.2e
5.1.2e

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

VITAL Vaccinating Elderly for Healthy Ageing

5.1.2e
5.1.2e
5.1.2e

WP2 particpipants

5.1.2e
5.1.2e
5.1.2e
5.1.2e

5.1.2e

imi innovative medicines initiative

efpia

nber 31