TKI Agri&Food
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Titel projectvoorstel: **1H4F-HEVentie: Hepatitis E virus intervention in primary pig production**

Nummer: **AF-18119**

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Het projectvoorstel past onder thema

☐ Consument & Maatschappij
√ Klimaatneutraal
√ Gezond & Veilig
☐ Circulair
☐ Slimme Technologie

Heeft u het voorstel ook elders ingediend? √ **Nee** ~~☐ **Ja, te weten bij ….**~~

Inhoudelijke beschrijving

1. Summary

Hepatitis E virus (HEV) is a viral zoonosis for which domestic pigs seem the most relevant reservoir for human infections. Pigs and humans normally do not show clinical signs of HEV infection, but hepatitis E can be life-threatening in human risk populations. Over the last years there have been increased human case numbers in Europe, evoking attention from public health authorities and the media. The latter caused public concerns regarding for instance the safety of pork and living nearby pig farms. Need for research in primary pig production to reduce risks has been stressed on several occasions in The Netherlands and Europe-wide. This PhD-project brings together a large consortium of actors in the Dutch pork supply chain to jointly address this need by developing and evaluating intervention measures in primary pig production to tackle HEV at the source. First serological assays will be validated and seroprevalence estimates will be obtained from ~200 farms to study variation in seroprevalence and identify high- and low-seroprevalence farms. Then risk factors will be identified from farms in these high- and low-cohorts by relating information from questionnaires and interviews to the presence or absence of HEV in pigs. A longitudinal study on four high- and low-seroprevalence farm will be conducted to determine the moment and cause of HEV-introduction on farms (guided by the identified risk factors) and to quantify the transmission dynamics within farms. These results will be used to model the effectiveness of on-farm intervention measures to lower the number of HEV-infectious pigs at slaughter. The most effective and feasible intervention measures will subsequently be applied on three high- and low-seroprevalence farms in a pilot scale to measure their effectiveness in practice. Project results will be communicated proactively through press releases, social

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media platforms and in professional and peer reviewed journals. This project is expected to ultimately lower the number of HEV shedding pigs arriving at slaughter, thereby improving food safety through a lower risk of contamination of food for human consumption, which will result in a lower incidence and disease burden in humans.

2. Intended aim

Problem

Hepatitis E gt3 and 4 (HEV) is a viral zoonosis for which the pig seems the most relevant reservoir for human infections. An estimated 50% of the Dutch fattening pig farms are infected with HEV at any given time and on average 70% of the animals become infected at some point during their lives (Rutjes et al., 2014). About 1 in 10 pigs still has an acute infection when it arrives at the slaughterhouse, which is accompanied by high numbers of virus particles in the liver. The remainder of the pigs that are infected on farms probably clears the virus before slaughter (NVWA, 2016). Pigs normally do not show overt clinical signs of HEV infection. In humans, HEV most often causes mild liver inflammation, but can be life-threatening in risk populations. Every year there are several hundreds of hospital admissions due to hepatitis E virus infections. Consumption of raw meat (EFSA, 2017), in particular dried pig sausage, or intensive contact with pigs gives an increased risk of HEV infection in humans (HEVIG study, RIVM, 2017, Bouwknegt et al., 2008).
In addition, donor blood infected with HEV poses a risk for humans (letter MinVWS to Health Council, May 2017). Since 2013, the human disease burden in The Netherlands has increased, from 50 to >300 cases annually, which cannot be explained solely by the increased attention paid to the infection in health care (letter Dutch Minister of Health to House of Representatives, Dec 2016). Also, in Europe an increase of human cases is observed.
Over the last years there has been an increased attention to human cases and their relationship with HEV in pigs, as demonstrated by two advices (upon joint request from minster of Health as well as Economic affairs) from the Expert committee on zoonosis in the Netherlands. Moreover, the Dutch Health Council will present a new advice on hepatitis E and blood donation in summer 2018. In addition, the Dutch Safety Board is expected to present the results of their investigation of food safety in the Netherlands by the end of the year, including HEV as one of their five case studies.
Next to the 'objective' risks, the virus regularly receives media attention (Brandpunt in 2015, Argos in 2017, 1Vandaag in 2017, national newspapers, etc.), raising concern among consumers about the safety of pork. In English media, HEV has recently been described as 'Brexit' virus, finger-pointing to pork imported from the Netherlands and Denmark as a source of British hepatitis E cases. In addition to concern about the safety of pork by citizens, such expressions also damage Dutch exports. Thus, in short, HEV in pigs has an impact on pork and the pig sector from different perspectives: real product safety for high-risk groups due to HEV contamination of meat, unnecessary loss of consumer confidence and negative consequences for exports. Currently, knowledge is lacking to provide a substantiated response to these aspects.
In 2018, the British Food Standards Agency organized a workshop with participants from all EU member states to identify necessary actions in the fight against HEV. Although there is a need for more knowledge about the management of HEV risks in the post-slaughter and the consumer phase, there is a strong demand for more knowledge about HEV control in the primary sector (FSA-EFSA stakeholder meeting, 2018 & MinVWS letter, 2017; see letters of support for HEVentie in Appendix V).
However, our knowledge about sources of introduction, the dynamics of transmission between and within pig farms shows considerable gaps. Recent research by a French group has identified a number of risk factors for HEV-carriage at slaughter, such as hygiene measures and the mixing of flocks. In addition, they suggest that there is an interaction between HEV and other viral infections that can influence the infection dynamics on a farm; i.e. a PRRSv infection could lead to a chronic HEV infection (Rose et al., 2017, Salines et al., 2015). Preliminary Polish results also suggest an association with farm hygiene (Niewitecki, 2018). Control measures can hardly be defined at this time. "HEVentie" aims to address these issues by identifying effective interventions for HEV infections on the farm (both breeding and fattening) and thereby reducing the number of HEV infected animals at slaughter, and therefore in pork. The ultimate goal is to be able to eliminate HEV on farms.

Goals and expected results

The primary goal of HEVentie is to enable HEV control on the primary farm, in order to reduce the number of HEV-contaminated pig carcasses at the slaughterhouse. This will directly increase the food safety of pork for HEV. For this, the following (partial) results are expected:

- Diagnostic tests have been evaluated for future use in a potential surveillance / monitoring program.

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- Risk factors have been identified for high prevalent farms, by comparing serological results of farms with high and low seroprevalence.
- The sources and the moment of HEV introduction are identified in finishing pig farms as well as the on-farm transmission dynamics at high and low risk fattening as well as multiplier farms.
- Effective HEV prevention and control measures have been identified and tested at the farm level.

3. Intended impact

For society, the intended impact of HEVentie will be:

- a lower number of HEV shedding pigs arriving at slaughter, thereby
- improving food safety through a lower risk of contamination of food for human consumption, which will
- result in a lower incidence and disease burden in humans.

We expect to achieve this this impact, because consumption of HEV infected pork (products) seems one of the main risk factors for humans to become infected. HEVentie will deliver the knowledge on HEV transmission within and between pig farms that will support the development and implementation (at pilot scale) of effective intervention measures.
For the sector, this project is expected to improve the general reputation of the pig industry by actively taking responsibility regarding a public concern. To make this visible, proactive public communication about the start of the project and intermediate results will be maintained. These activities will contribute positively to the license to produce of the pork sector.
For each of our consortium partners there are additional stakes: either direct by enabling support to farmers in mitigating HEV and the better marketing of pigs (LTO/ POV) and pork (Vion) as well as pork products (Vion, COV-VNV), or indirect by increasing demand for diagnostic tests and monitoring programs (ThermoFischer, GD Deventer) and for potential effective intervention measures (MS Schippers, IDT-Biologika). The consortium is strengthened by cooperation of knowledge and teaching institutes (WVBR, UU and HAS) as well as farmers' organizations (LTO / POV) that will enable rapid scaling-up of the implementation of intervention measures by education and training of (future) pig consultants and veterinarians using the knowledge developed in this consortium. The project thereby contributes to a more efficient knowledge transfer and implementation in the field.
For the scientific community the output of HEVentie is expected to generate detailed and robust data regarding on-farm introduction and transmission of HEV, supporting further risk assessments and enabling the development of future novel intervention measures (e.g. vaccines) to lower HEV transmission. Currently it is unknown where in farms the main propagation and transmission events of the virus take place, nor what risk factors affect this propagation and transmission.

4. Project approach

Global approach

This project consists of six work packages (WP1-6). After every 12 months there will be an evaluation moment on the project progress and continuity. For a detailed description of the workplan, please refer to Appendix 2 and 3.

WP1. A cross sectional study will be performed to determine the variation in prevalence between farms of pigs that are slaughtered with a (historical) HEV infection. High variation will indicate that opportunities for intervention exist. Twenty-seven blood samples from 200 farms will be collected to distinguish an 80% seroprevalence from a 20% seroprevalence with 95% confidence and 15% error rate. Samples will be collected at the slaughterhouse from fattening pigs as well as breeding sows. A stratum of so-called 'high-care' farms is included among the 200 farms to already provide a direction of intervention opportunities. At 'high-care' farms an optimal biosecurity protocol and an optimal housing (e.g. coated flooring and fencing) is in place. Furthermore, a stratum of PRRSv free herds will be included to examine the effect of co-infection on HEV-seroprevalence. And lastly, a stratum of organic farms will be included to study whether increased environmental exposure affects the seroprevalence.

Go-No go decision: absence of variation leads to project termination or amended plans, in consultation with all parties.

WP2. This WP focuses on the performance of two serological assays, one in-house ELISA from WBVR and one commercially available ELISA. A proper understanding of the performance of the ELISA will enable the selection of the

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best performing test for the remaining WPs. In view of future HEV surveillance programs or on-demand testing, such a test is needed. A subset of ~900 serum samples will be analysed with both assays, subsequently employing Bayesian latent class analyses to overcome the issue of absence of a gold standard (e.g. Joseph et al., 1995). Here, HEVentie can affiliate with an existing PhD project "Zoonotic risks of HEVS from swine reservoirs" at the WBVR (supervised by W. van der Poel and Mart de Jong, WU), where both project will benefit from the interaction.

WP3. In WP3, a case-control study will be conducted to further identify and specify risk factors and control measures. Two strata of 50 high- and 50 low-seroprevalence farms, selected from WP1, are visited by the PhD student and/or a trained group of HAS students. A standardized questionnaire and semi-structured interview is used during a farm audit, detailing e.g. the cleaning and disinfection procedures, the animal flow management and presence of co-infections (at least PRRSv and Swine Influenza Virus (SIV)). A sample of the high-care stratum will also be included in WP3.

WP4. This WP consists of a longitudinal study to investigate the moment and cause of introduction as well as the infection dynamics of HEV on farms. For this study eight farms will be selected: four high-seroprevalence and four low-seroprevalence farms from WP3. Twenty sows and 10 pigs per litter from two cohorts per farm will be sampled (blood and faeces) on at least five moments. Two groups of four farms are expected to provide sufficient power to identify differences, because each farm includes a repetition that adds power in the hierarchical modelling. The intensive monitoring on these farms will also allow further investigation in specific risk management measures and concurrent infections (e.g. PRRSv and SIV). Quantification of the transmission dynamics in combination with simulation modelling will identify relevant transmission and intervention points in time and place during the pig production cycle.

WP5. This WP consists of a pilot intervention study on three high-risk farms from WP3 and WP4 to test the potentially effective interventions identified in WP4. The design is similar to WP4. Although no specific measures are aimed for yet, examples of interventions could be the control of concurrent infections with PRRSv/SIV (Rose et al.,2018), specific hygiene interventions to reduce within farm transmission, or reduce the risk of introduction to the farm.

WP6. Communication phase. The project and its results will be proactively communicated to show the sectors involvement and cooperation within a large consortium on this issue. For further details on communication, please see under heading 6.

5. Organisation

The HEVentie consortium will be organised on three levels. An advisory board will be constituted after the project has been awarded, consisting of external representatives of the financing parties. The advisory board will meet at least once a year and will specifically be consulted on the go-no go decision point and evaluations moments.

Strategic consortium meetings, for all consortium partners, will be organised each four months to discuss project results and progress, and decide on potential amendments of project plans on the long term. The strategic consortium will have an informative task to the advisory board, at least on the go-no go moments.

Day-to-day activities will be managed by the project management team of HEVentie, comprised by the (daily) supervisors of the PhD student (Prof Arjan Stegeman, Prof Wim van der Poel, Dr. Tijs Tobias, Dr. Martijn Bouwknegt). The HEVentie consortium foresees to recruit a PhD student who will perform most of the practical work regarding data collection and analysis and reporting. The PhD student will be based at Utrecht University, but will regularly work from Vion in Boxtel or WBVR in Lelystad as well. Depending on the project stage relevant consortium partners will be invited for management meetings; i.e. when farms need to be visited in stage III, the HAS representative will attend the meetings to discuss strategic and practical issues in this respect. Support to the PhD student in the practical activities will be provided by students from the HAS.

6. Communication

The consortium will pursue a proactive communication strategy. At the start of the project, a press statement will be released to introduce the project. Social media, websites and newsletters from partners will be used, where possible and

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relevant, to report on the progress and findings of HEVentie. Furthermore, new knowledge that is being developed within HEVentie will be communicated in a wide variety of means to relevant stakeholders and consortium partners.

- Professional publications will be produced and offered to farmers' journals and websites.
- Scientific abstracts will be submitted for presentations at relevant conferences, such as ESPHM and ECVPH meetings.
- At least four scientific publications will be submitted for international peer reviewed scientific publication (in English).
- Relevant stakeholders, if not already involved in the consortium, on HEV in The Netherlands (e.g. RIVM, other departments of the Faculty of Veterinary Medicine and Wageningen UR, Sanquin and the Ministry of Agriculture, Nature and Food quality as well as the Ministry of Health Welfare and Sports) will be actively informed by forwarding consortium results in an early stage.

In addition we will organise at least two workshops for farm consultants and account managers of slaughterhouses as well as for veterinarians and the topic will be addressed at least at one national scientific meeting for swine veterinarians (established cooperative structure in place by GD Deventer, UU and KNMvD).

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Tabel 1. Project budget

Projectcosts			Costs in k€ EXCLUDING VAT				
			2019	2020	2021	2022	Total
Personele kosten voor inzet onderzoekers:							
Knowledge institutions / public partners	**function**	**fte**	**108.9**	**99.2**	**99.2**	**88.1**	**395.4**
WBVR/DLO (Prof. dr. WHM vd Poel)	Senior scientist / PhD supervisor	0.025	6.4	6.4	6.4	6.4	25.6
WBVR/DLO	Lab technician	variable	41.5	31.8	31.8	20.7	125.8
Univ Utrecht (Dr. T Tobias)	Project coordination	0.05	6.0	6.0	6.0	6.0	24.0
Univ Utrecht (PhD student)	AIO	1	55.0	55.0	55.0	55.0	220.0
Private commitment (in kind)	**hours**	**Tariff**	**33.4**	**43.0**	**33.4**	**33.4**	**143.2**
GD Deventer (M Houben/L Dieste Perez)	25	60	1.5	1.5	1.5	1.5	6.0
Vion (Dr. M Bouwknegt) + sampling yr 1	80	60	4.8	4.8	4.8	4.8	19.2
MS Schippers (J van Iersel)	25	60	1.5	1.5	1.5	1.5	6.0
ThermoFischer (P Buholzer)	25	60	1.5	1.5	1.5	1.5	6.0
IDT-Biologika (Dr. P vd Wolf)	25	60	1.5	1.5	1.5	1.5	6.0
COV/VNV (R vd Kruijk / R de Mooij)	25	60	1.5	1.5	1.5	1.5	6.0
LTO / POV (Producenten Organisatie varkenshouderij (H.Prinsen / A van Lenthe / L Janssen)	35	60	2.1	2.1	2.1	2.1	8.4
WUR (Prof. M de Jong)	10	60	0.6	0.6	0.6	0.6	2.4
Univ Utrecht (Prof. dr. JA Stegeman)	80 (PhD supervisor)	140	11.2	11.2	11.2	11.2	44.8
Univ Utrecht(Dr. T Tobias)	80	75	6.0	6.0	6.0	6.0	24.0
HAS DB (Dr. J vd Borne) (extra hours in yr 2)	20	60	1.2	10.8	1.2	1.2	14.4
Other			**0.0**	**0.0**	**0.0**	**0.0**	**0.0**

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TOTAL PERSONNEL:			**142.3**	**142.2**	**132.6**	**121.4**	**538.6**
Material cost and services by third partners:							
Knowledge institutions / public partners			**28**	**2**	**66**	**18**	**114.7**
WBVR/DLO	lab analyses material and diagnostic tests		24.6	1.9	66.4	18.4	111.2
Univ Utrecht	animal welfare license fees and handling		3.5	0.0	0.0	0.0	3.5
WUR			0.0	0.0	0.0	0.0	0.0
HAS DB			0.0	0.0	0.0	0.0	0.0
Private inzet (in kind)			**15**	**0**	**11**	**9**	**36.1**
Gezondheidsdienst voor Dieren	logistics + storage samples		1.8	0.0	0.0	0.0	1.8
Vion	slaughterhouse sampling		7.3	0.0	0.0	0.0	7.3
MS Schippers	WP5: intervention materials		0.0	0.0	0.0	6.0	6.0
ThermoFischer	50% of diagnostic tests in kind contribution		1.8	0.0	9.5	3.5	14.7
IDT	diagnostics on concurrent infections SIV		5.4	0.0	1.8	0.0	7.2
COV/VNV			0.0	0.0	0.0	0.0	0.0
LTO / POV			0.0	0.0	0.0	0.0	0.0
TOTAL MATERIAL:			**44.4**	**1.9**	**77.6**	**27.8**	**151.8**
Investment in equipment and depreciation:							
Knowledge institutions / public partners			**0**	**0**	**0**	**0**	**0.0**
None							0.0
Private commitment (in kind)			**0**	**0**	**0**	**0**	**0.0**
None							0.0
Other			**0**	**0**	**0**	**0**	**0.0**
None							

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TOTAL INVESTMENT:			**0**	**0**	**0**	**0**	**0.0**
Other costs, travel expenses, etc.							
Knowledge institutions / public partners			**2**	**7**	**4**	**2**	**16,0**
WBVR/DLO	Travel expenses		0.15	0.15	0.15	0.15	0.6
Univ Utrecht	PhD travel expenses + farm visits		1.40	4.25	4.14	2.09	11.9
HAS DB	Farm visits		0.15	3.00	0.15	0.15	3.5
Private in kind			**1.3**	**1.3**	**1.3**	**4.3**	**8.3**
Gezondheidsdienst voor Dieren	Workshops + travel expenses		0.15	0.15	0.15	3.15	3.6
Vion	Travel expenses		0.15	0.15	0.15	0.15	0.6
MS Schippers	Travel expenses		0.15	0.15	0.15	0.15	0.6
ThermoFischer	Travel expenses		0.15	0.15	0.15	0.15	0.6
IDT	Travel expenses		0.15	0.15	0.15	0.15	0.6
COV/VNV	Travel expenses		0.15	0.15	0.15	0.15	0.6
LTO / POV	Travel expenses		0.40	0.40	0.40	0.40	1.6
Other			**10.0**	**10.0**	**10.0**	**10.0**	**40.0**
unforeseen (~5%)			10.0	10.0	10.0	10.0	40.0
TOTAL OTHER:			13	19	16	17	64.2
COSTS TOTAL (excl. VAT):			**200**	**163**	**226**	**166**	**754.6**

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Tabel 2. Projectfinanciering

Projectinkomsten	**Offered / requested amounts (k€)**				
	2019	**2020**	**2021**	**2022**	**Total**
Total offered by companies *in kind*	49.7	43.0	44.6	42.9	180.2
Total offered by companies *in cash*	52.5	52.5	52.5	52.5	210.0
Requested public financing	97.5	67.3	128.9	70.6	364.4
TOTAL (excl. VAT)	**199.7**	**162.8**	**226.0**	**166.0**	**754.6**

Remark: The WR-capacity includes a small amount dedicated to the travel costs for HAS students, HAS employees and the PhD student, as well as an amount for project coordination by Utrecht University.

Tabel 3. Specification of *in-kind* private contributions per company

The specification is already part of Table 1. A detailed Excel-file is available on request.

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Tabel 4. Specification of the *in cash* private contributions per company

Name Partner	For which public partner?	MKB	Amount of in cash (k€)				
			2019	2020	2021	2022	Total
Gezondheidsdienst voor Dieren	Utrecht University	~~JA/~~NEE	7.5	7.5	7.5	7.5	30,0
Vion	Utrecht University	~~JA/~~NEE	7.5	7.5	7.5	7.5	30,0
MS Schippers	Utrecht University	~~JA/~~NEE	7.5	7.5	7.5	7.5	30,0
ThermoFischer	Utrecht University	~~JA/~~NEE	7.5	7.5	7.5	7.5	30,0
IDT-Biologika	Utrecht University	~~JA/~~NEE	7.5	7.5	7.5	7.5	30,0
Dutch Meat Association (COV)	Utrecht University	~~JA/~~NEE	3.75	3.75	3.75	3.75	15,0
Dutch Meat Products Association (VNV)	Utrecht University	~~JA/~~NEE	3.75	3.75	3.75	3.75	15,0
LTO / POV (Producenten Organisatie varkenshouderij)	Utrecht University	~~JA/~~NEE	7.5	7.5	7.5	7.5	30,0
TOTAL excl. VAT			**52.5**	**52.5**	**52.5**	**52.5**	**210.0**

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Handtekening(en) voor akkoord:

Namens 1H4F consortium: ZLTO

Naam: Jeannette van de Ven

Handtekening:

Datum: 28 – 9 - 2018

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Handtekening(en) voor akkoord:

Kennisinstelling: ~~WVBR~~ Stichting Wageningen Research

Naam: ~~Dr. Tjeerd Kimman~~ Drs. Ir. M.T. van Manen

Handtekening:

Datum: 28-6-2018

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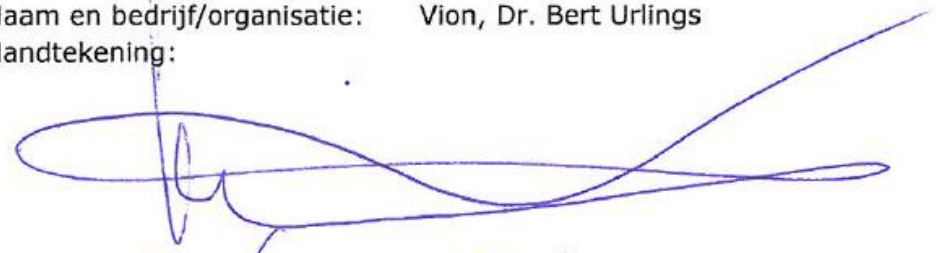
Handtekening(en) voor akkoord:

Private trekker: Vion

Naam en bedrijf/organisatie: Vion, Dr. Bert Urlings

Handtekening:



Datum: 29-6-2018

Vion
FOOD GROUP

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Letter of intent

With this letter of intent, the partner indicated below expresses the willingness to contribute to 'HEVentie' as described in the project proposal. Executive approval will be obtained when the project is granted and will be formalized by the Consortium Agreement.

Partner:

Name: Mark Schippers

Date & place: 29-06-2018, Bladel

Signature:

Tegen de uitspraak van TKI Agri&Food over de beoordeling van de PPS-aanvraag is geen beroep mogelijk; met het indienen van deze aanvraag accepteert u dit.

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Partner: **Utrecht University**

Name: drs. G.J. Tillemans

Date & place: Utrecht, June 2018

Signature:

Tegen de uitspraak van TKI Agri&Food over de beoordeling van de PPS-aanvraag is geen beroep mogelijk; met het indienen van deze aanvraag accepteert u dit.

Letter of intent

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Partner: GD BV

Name: L. Eland

Date & place: Deventer, June 28th

Signature:

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Veilig voedsel produceren

Topsector Agri& Food

TKI Agri&Food
Postbus 557
6700 AN Wageningen
www.tki-agrifood.nl

Letter of intent

With this letter of intent, the partner indicated below expresses the willingness to contribute to 'HEVentie' as described in the project proposal. Executive approval will be obtained when the project is granted and will be formalized by the Consortium Agreement.

Partner: Thermo Fisher Scientific

Name: Patrik Buholzer

Date & place: Schlieren, 26th June 2018

Signature: 

Tegen de uitspraak van TKI Agri&Food over de beoordeling van de PPS-aanvraag is geen beroep mogelijk; met het indienen van deze aanvraag accepteert u dit.

Letter of intent

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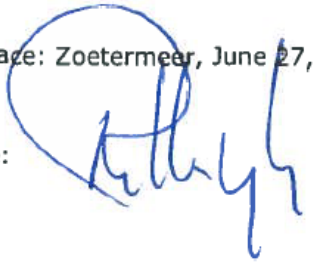
Partner: Dutch Meat Association (COV)

Name: Richard van der Kruijk

Date & place: Zoetermeer, June 27, 2018

Signature:



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Partner: Dutch Meat Products Association (VNV)

Name: Richard van der Kruijk

Date & place: Zoetermeer, June 27, 20182

Signature:

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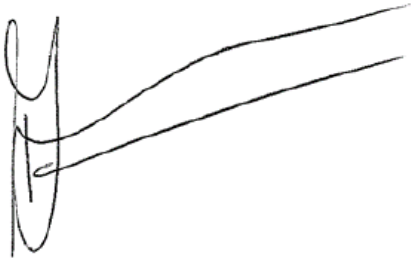
Partner:

Name: Ingrid Jansen, voorzitter Producenten Organisatie Varkenshouderij (POV)

Date & place: Ede, 28 juni 2018

Signature:



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Partner:

Name: *IDT Biologika*

Date & place: *29 June 2018, Deventer*

Signature:

Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

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Ons kenmerk
00003/2018\JvD\LH
Uw kenmerk
Kopie aan

Bijlage(n)

Datum 26 juni 2018
Betreft Support for the PPS project proposal "HEVentie"

To Whom It May Concern,

This letter is to inform you that the Centre for Infectious Disease Control of The Netherlands as part of the National Institute for Public Health and the Environment (RIVM Bilthoven), hereafter referred to as CIb, enthusiastically supports the 1Health4Food Project "Hepatitis E virus intervention in primary pig production", that will be submitted to TKI Agri&Food for funding as Public Private Partnership.

The CIb is the centre that in The Netherlands coordinates the control of infectious diseases, including effective prevention, close vigilance, preparedness and response for both endemic infectious diseases as well as in the event of an outbreak, with the goal to reduce the impact of health problems related to infectious diseases. One such infectious disease is the hepatitis E virus and CIb contributes to HEV control by several initiatives: CIb has organized several 'One Health' expert consultations on hepatitis E virus due to the recent increase in (mainly asymptomatic) human case reports, has provided support in answering ministerial questions on HEV and has initiated studies to generate epidemiological knowledge, including a case-control study among humans (the HEVIG-study – investigating the role of various food products as source of infection). Insights generated in amongst other the latter study confirm the importance of tackling HEV at the source, which are the domestic pigs. However, data gaps still exist to make the step towards effective intervention measures on pigs farms. For that reason, the CIb supports the project 'HEVentie' so that effective intervention measures can be developed and their effectiveness in the field indicated.

Sincerely,

Prof. dr. Jaap T van Dissel
director, Centre for Infectious Disease Control Netherlands
National Institute for Public Health and the Environment

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Appendix 1: overview of all participating PPS-partners

Naam partner 1	Wageningen BioVeterinary Research, Wageningen University
KvK nr.	09215846
Postadres en postcode	Houtribweg 39
Plaats	Lelystad
Contactpersoon	Wim van der Poel
e-mailadres	wim.vanderpoel@wur.nl

Naam partner 2	Utrecht University
KvK nr.	30275924
Postadres en postcode	Heidelberglaan 8, 3584 CS
Plaats	Utrecht
Contactpersoon	Drs. Geert Tillemans (director) / Arjan Stegeman (Promotor)
e-mailadres	g.j.tillemans@uu.nl / j.a.stegeman@uu.nl

Naam partner 3	University of Applied Sciences Den Bosch
KvK nr.	41084408
Postadres en postcode	Onderwijsboulevard 221, 5223 DE
Plaats	's Hertogenbosch
Contactpersoon	Joost van den Borne
e-mailadres	j.vandenborne@has.nl

Naam partner 4	Animal Health Service
KvK nr.	8117636
Postadres en postcode	Arnsbergstraat 7, 7400 AA
Plaats	Deventer
Contactpersoon	Manon Houben
e-mailadres	m.houben@gddiergezondheid.nl

Naam partner 5	Vion Food
KvK nr.	16078870
Postadres en postcode	Postbus 1, 5280 AA
Plaats	Boxtel
Contactpersoon	Martijn Bouwknegt
e-mailadres	martijn.bouwknegt@vionfood.com

Naam partner 6	Schippers Europe BV
KvK nr.	17042016
Postadres en postcode	Rond Deel 12, 5531 AH
Plaats	Bladel
Contactpersoon	Joris van Iersel
e-mailadres	j.vaniersel@schippers.eu

Naam partner 7	ThermoFischer
KvK nr.	39074495
Postadres en postcode	Platinastraat 33, 8211 AR
Plaats	Lelystad
Contactpersoon	Patrik Buholzer
e-mailadres	patrik.buholzer@thermofisher.com

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Naam partner 8	IDT-Biologika
KvK nr.	58659838
Postadres en postcode	Cerresstraat 13, 4811 CA
Plaats	Breda
Contactpersoon	Peter van der Wolf
e-mailadres	peter.vanderwolf@idt-biologika.com

Naam partner 8	Vereniging voor de Nederlandse Vleeswarenindustrie (VNV)
KvK nr.	40408071
Postadres en postcode	Postbus 64, 2700 AB
Plaats	Zoetermeer
Contactpersoon	Richard van der Kruijk
e-mailadres	rvdkruijk@cov.nl

Naam partner 9	Centrale Organisatie voor de Vleessector (COV)
KvK nr.	40410403
Postadres en postcode	Postbus 61, 2700 AB
Plaats	Zoetermeer
Contactpersoon	Richard de Mooij
e-mailadres	rdmooij@cov.nl

Naam partner 10	POV / LTO (Producenten Organisatie Varkenshouderij)
KvK nr.	61024341
Postadres en postcode	Zwartewaterallee 14 8031DX
Plaats	Zwolle
Contactpersoon	Linda Janssen / Heleen Prinssen
e-mailadres	ljanssen@pov.nl / heleen.prinsen@zlto.nl

Naam partner 11	Wageningen Universiteit
KvK nr.	09215846
Postadres en postcode	Droevendaalsesteeg 3
Plaats	Wageningen
Contactpersoon	Mart de Jong
e-mailadres	mart.dejong@wur.nl

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Appendix 2: detailed multi-annual workplan

This project consists of several workpackages (WPs) that each detail a specific part of HEVentie. The work will be carried out in four years' time (see Fig. 1). Each WP will be explained in detail in the following segments.

WP0 Project coordination

Project coordination will be executed by Utrecht University. This will comprise the overview of responsibilities and tasks and planning of activities. Moreover, Utrecht University will be responsible for obtaining relevant licenses for animal experimentation for phase I (farms specifically from strata that do not deliver to private party 1), phase IV and V.

WP1. Screening phase

A cross sectional study will be performed to determine the variation in prevalence among farms of pigs that are slaughtered with a (historical) HEV infection. This variation is an important indicator of the progress that can be achieved in the remainder of the project. High variation indicates clear opportunities for improvement and vice versa. The sampling frame (N=200 farms; Fig. 2) and sample size per farm (27 samples over a 6 month period; Fig. 3) will enable to differentiate farms with a 80% seroprevalence from farms with a 20% seroprevalence with 95% confidence and 15% error rate. To this end, HEVentie will connect to an existing sampling infrastructure that is in place for monitoring of Toxoplasma and Mycobacterium at Vion. This monitoring includes fattening pigs and breeding sows and thus provides a picture of both the breeding and finishing pigs. From each of these farms, six blood samples per delivery at the slaughterhouse will be obtained over an extended period until in total 27 samples (i.e., five deliveries) per farm have been obtained. In addition, a stratum of so-called 'high-care' farms is included (Fig. 2).

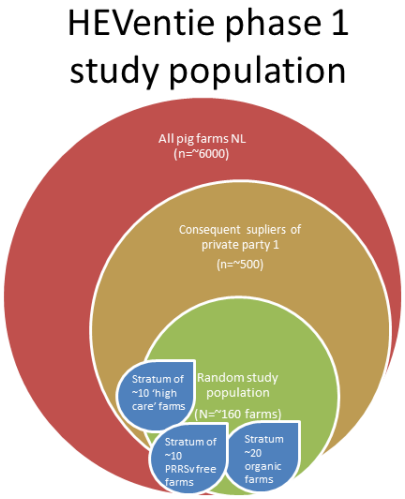

Figure 2: HEVentie WP1 study population relative to pig farming in The Netherlands

At 'high-care' farms an optimal biosecurity protocol and an optimal housing (e.g. coated flooring and fencing) is in place. Moreover, strata will also be comprised of (<20) farms free from PRRSv, as PRRSv is hypothesized to promote HEV infection (Rose, et al., 2018), and (20) organic farms, as pigs on these farms have more frequent environmental exposure. The hypothesis is that high care farms and the PRRSv-free farms will deliver a relatively low proportion of HEV seropositive and virus positive pigs to slaughter and for organic farmers the hypothesis is the opposite.

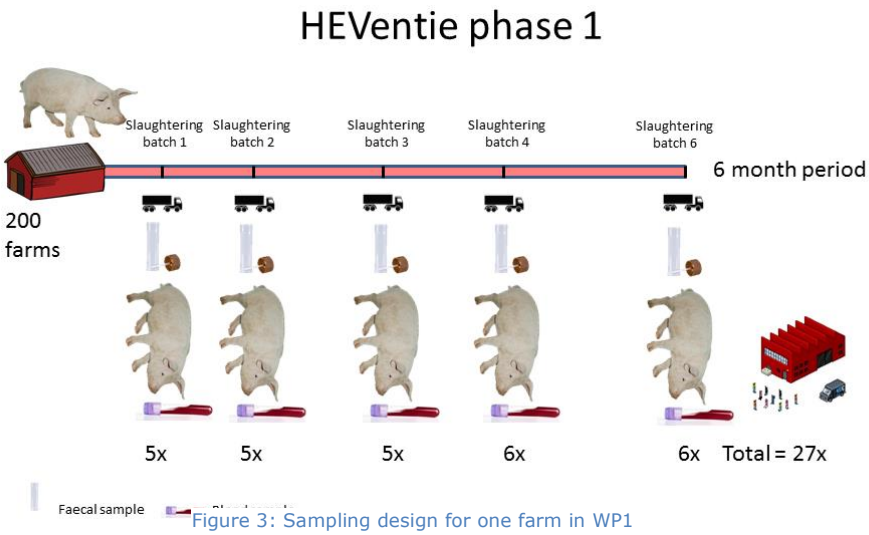

Figure 3: Sampling design for one farm in WP1

WP2. Diagnostic test evaluation.

WP2 will be executed concurrently with WP1 (Fig. 1). It may be expected that a HEV surveillance program will be in place in the future. However, also in HEVentie WP4 preferably the most suitable and (cost-)efficient test will be used. To this end we will evaluate two diagnostic serological assays to select the preferred test and to allow the design of a surveillance program to be carried out in parallel to WPs 3, 4 and 5. Here, an existing PhD project "Zoonotic risks of HEVS from swine reservoirs" at the WBVR (supervised by W. van der Poel and Mart de Jong, WU) will be affiliated. For

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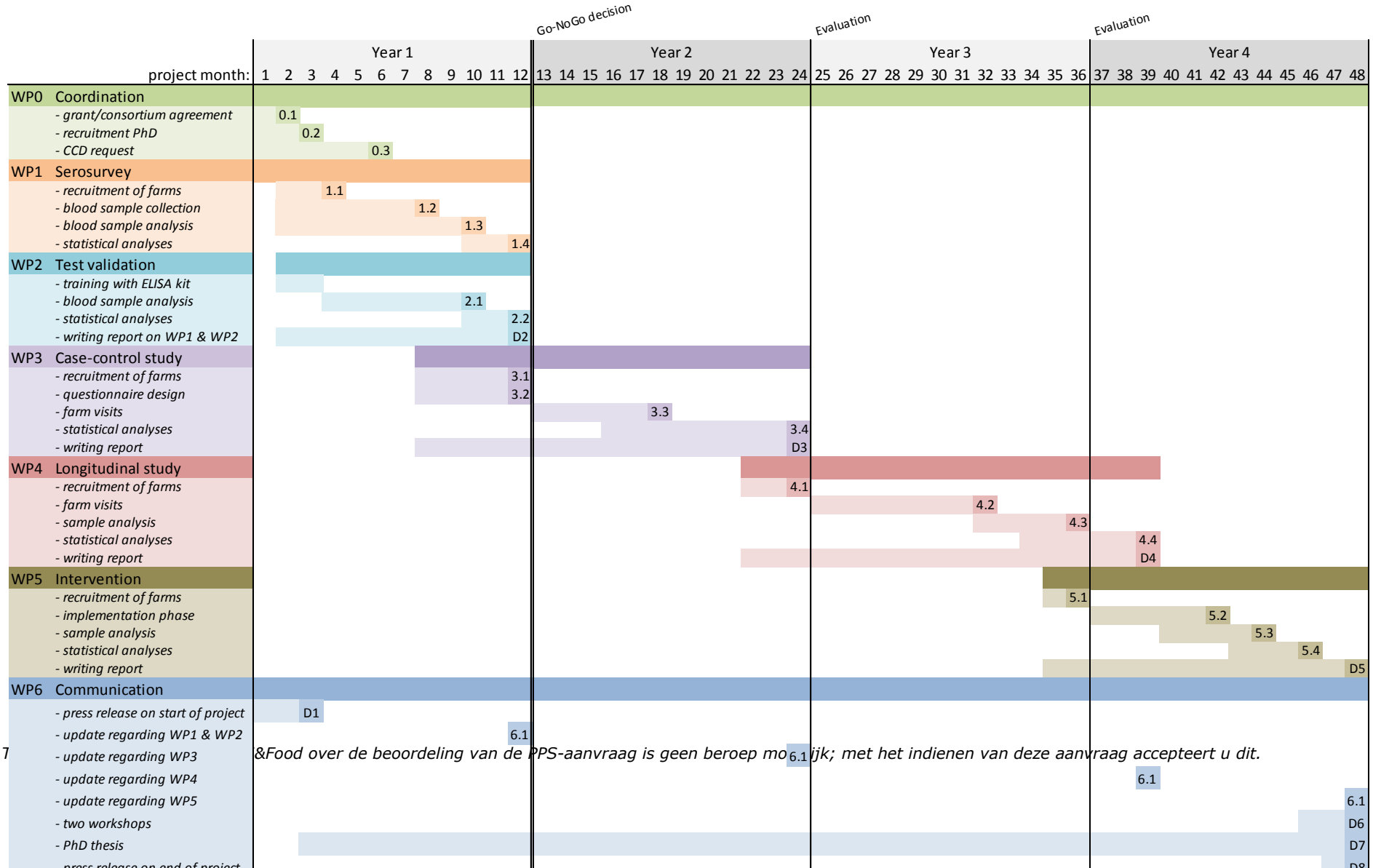
the statistical analysis of diagnostic test comparison Bayesian latent class analyses will be used to overcome the issue of absence of a gold standard (e.g. Joseph et al., 1995).



T &Food over de beoordeling van de PPS-aanvraag is geen beroep mo ijk; met het indienen van deze aanvraag accepteert u dit.

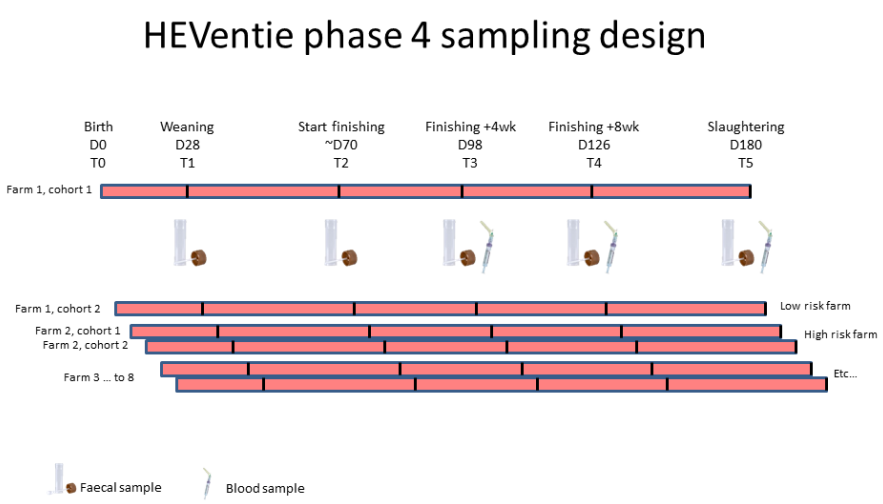
WP3. Case-control study

A case-control study will be conducted to identify risk factors for HEV infection and possible control measures. Two strata will be selected from phase I, each comprising 50 farms, based on a high or low seroprevalence. These farms will be visited by either the PhD student and/or a trained group of HAS students. A standardized questionnaire and semi-structured interview will be used during a farm audit, including for example, details on the cleaning and disinfection procedures, the animal batch flow management and presence of concurrent infections (at least PRRSv and e.g. Influenza). The output of this phase will be the identification of risk factors and potential intervention strategies that are more frequently observed in one stratum compared to the other.

Evaluation moment (~24 months) In case no risk factors can be identified that are to be influenced through intervention measures, then the project will be amended after careful consideration with the advisory board, all parties and the 1Health4Food advisory group.

WP4. Cohort study phase

A longitudinal study, to further investigate the introduction and infection dynamics of HEV on the farm, will be performed. For this study eight farms will be selected: four high-prevalence and four low-prevalence farms from WP3. Approximately 20 sows and their litters from two cohorts per farm will monitored. Pigs will be sampled at at least five points in time: weaning (25 days), start of grower phase (70d), four and eight weeks later (98d and 126d) and at slaughter (180d). This frequency and timing will provide sufficient insight to model the on-farm transmission. The aim will be to identify the moment and cause of introduction of HEV in litters and cohorts. Faecal and blood samples (on a selection of sampling occasions) will be collected and analysed for the presence of HEV (PCR) and/or antibodies (ELISA) (for details see Figure 4).



To lower the costs of analyses, samples will be pooled on litter level for PCR analysis and in case of positive results, individual samples will be tested. Per cohort, 20 sows and 10 pigs per litter will be tested, summing up to a total of 572 serum samples per farm and 300 PCR samples per farm (assuming that 20% of litters returns a positive virus sample and need individual retesting) (Fig. 5). Two groups of 4 farms are expected to provide sufficient power to identify differences (that are big based on the information from the previous phases), because each farm includes a repetition that can be used in the data analysis, provided hierarchical modelling is applied.

Figure 4: HEVentie WP4 sampling design cohort study

Introductions of HEV in farms or pens will be identified and the in- and decrease in numbers of HEV shedding pigs and seropositive pigs over time will be investigated. Relevant differences between the high-prevalence and low-prevalence farms will be assessed using advanced statistical and mathematical modelling. The intensive monitoring on these farms will also allow for further investigations in specific risk management measures and concurrent infections (e.g. PRRSv and Swine Influenza Virus). Quantification of the transmission dynamics in combination with simulation modelling will identify relevant transmission and intervention points in time and space during the pig production cycle. Simulation modelling also enables to study *in silico* the effect of interventions on the number of HEV positive pigs at slaughter.

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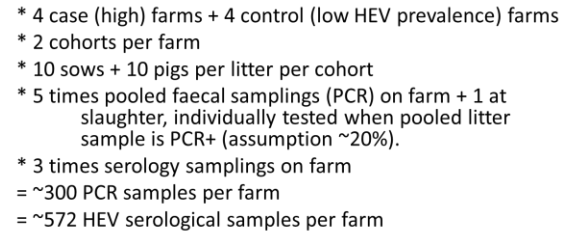

Figure 5: sample numbers HEVentie in WP4

Evaluation moment (~36 months). In case phase IV results in clear manageable and feasible intervention measures, in WP5 a pilot study will be conducted. In case no intervention measures can be identified, all parties will be consulted to whether or not phase V should commence or the project should be amended.

WP5. Implementation of intervention measures at pilot scale

This WP consists of a pilot intervention study on three high-risk farms from WPs 3 and 4 to test the potentially effective interventions identified in phase IV under field conditions. Again, per farm two cohorts will be followed, while in the mean time they apply an intervention as defined by the consortium partners. As interventions likely will need to be applied on batch / cohort level, in this case we can only use the data of WP3 and WP4 of the same farm as historical control. Consequently, this intervention study merely serves as a pilot project to evaluate whether effective interventions can be identified, and which measures are feasible for testing in a future project. Although no specific measures are aimed for yet, examples of interventions could be the control of concurrent infections with PRRSv (Rose et al.,2018), specific hygiene interventions to reduce within farm transmission (such as cleaning and disinfection, or disinfection of water installation to specific animal batch management, or reduce the risk of introduction to the farm (external biosecurity, animal purchasing policies, transport). The identification of the specific set of measures will be performed with the whole consortium.

WP6. Project communication

Results and knowledge about effective HEV interventions are communicated widely via the partners to pig farmers, business consultants, agricultural education institutions and universities, among others through (professional) publications and two workshops for farm consultants and account managers.

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Appendix 3: Workplan, activities, milestones and deliverables of HEVentie

WP	*Due date (month)*	*Activity*	*Milestone or deliverable*	*Partners responsible*
0	2	Consortium agreement	M0.1 Consortium agreement signed	WBVR
	3	Recruitment of PhD student	M0.2 PhD student recruited	UU, WBVR, Vion
	6	Application for license on animal welfare research (METC)	M0.3 Licence obtained for animal welfare research	UU
1	4	Recruiting farms to obtain blood samples from pigs at slaughter (all strata)	M1.1 farmers recruited	Vion
	8	Collection of blood samples	M1.2 blood samples collected at slaughter (~5400x)	Vion, GD
	10	Analyses of blood samples by serology	M1.3 laboratory results obtained	WBVR
	12		M1.4 variation in HEV seroprevalence and HEV shedding between farms determined	UU
2	11	Evaluation of analysis methods	M2.1 test evaluation completed	WBVR, ThermoFischer
	12	Statistical analyses	M2.2 choice of test for further work in HEVentie determined	WBVR, UU
	12	Manuscript preparation on WP1&2 results	D2: manuscript on test comparison and variation in seroprevalence	All
	12	*Go-no go decision*	*decision on go-no go to proceed with consortium plans*	All
3	12	Designing questionnaire for WP2	M3.1 questionnaire ready for use	UU, HAS
	12	Recruitment of farms	M3.2 farmers recruited	Vion
	18	Performing interviews at farms (100x)	M3.3 questionnaire answers collected and analysed	HAS, UU
	24	Statistical analyses of questionnaire results	M3.4 risk factors identified for low HEV seroprevalence	UU
	24	Manuscript preparation on WP3 results	D3 manuscript on potential risk factors	All
	24	*Evaluation moment*	*decision on how to proceed with consortium plans considering the results*	All
4	27	Recruiting farms for longitudinal study	M4.1 farmers recruited	Vion
	32	Performing longitudinal study on farms	M4.2 practical aspect of longitudinal study completed, samples collected	UU, HAS
	36	Analyses of samples	M4.3 all sample results obtained	WBVR
	39	Statistical analyses of results	M4.4 potential intervention measures and moments identified	UU
	39	Manuscript preparation on WP4 results	D4 manuscript on longitudinal study	
	36	*Evaluation moment*	*decision on go-no go to proceed with phase 4*	All
5	36	Recruiting farms for intervention study	5.1 farms recruited	Vion
	42	Performing intervention study	5.2 interventions in place, samples collected,	UU/HAS + MS Schippers
	44	Sample analysis	5.3 samples analysed	WBVR
	46	Statistical analyses		
	48	Manuscript preparation on WP4 results	D5 manuscript on intervention study	

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WP	Due date (month)	Activity	Milestone or deliverable	Partners responsible
6	3	Press release on project start	D1 press release on project start	
	12	Communication on results of WP1&2	M6.1 communication on results of WP1&2	UU/Vion
	24	Communication on results of WP3	M6.2 communication on results of WP3	UU/WBVR
	39	Communication on results of WP4	M6.3 communication on results of WP4	UU/WBVR
	48	Communication on results of WP5	M6.4 communication on results of WP5	UU
	48	Workshops for farm consultants and vets	D6 Two workshops held	GD/Vion
	48	Communication of consortium results to professional and other non-scientific means	>2 professional publications on consortium results published	GD/HAS
	48	Finalising PhD thesis	D7 PhD thesis finalised and date for defence has been set	UU
	48	Press release on end of project	D8 Press release on end of project	

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Appendix IV: References HEVentie

- Rutjes SA, Bouwknegt M, van der Giessen JW, de Roda Husman AM, Reusken CB. Seroprevalence of hepatitis E virus in pigs from different farming systems in The Netherlands, J Food Prot. 2014 Apr;77(4):640-2. doi: 10.4315/0362-028X.JFP-13-302

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- letter Minister of Health Welfare and Sports to Dutch Health Council, 15 May 2017, https://www.gezondheidsraad.nl/sites/default/files/adviesaanvraag_1138813_bloeddonaties_en_hepatitis_e-virus.pdf

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- Brandpunt in 2015, https://brandpuntplus.kro-ncrv.nl/brandpunt/opmars-van-gevaarlijk-virus-overgedragen-door-varkens/

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- Joseph L, Gyorkos TW, Coupal L. Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. Am J Epidemiol 1995; 141 (3): 263-272.

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Letters of intent and support: See above

Consortium partners – letter of intent

- Utrecht University
- Gezondheidsdienst voor Dieren
- Vion
- ThermoFischer
- COV
- VNV
- POV / LTO
- MS Schippers
- HAS Hogeschool
- IDT Biologica

Stakeholders – letters of support

- RIVM / Centre of Infectious Disease Control Netherlands
- European Food Safety Authority, Italy (expected July 2nd)
- Food Standards Agency, UK (expected week 27)

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