**Annex 1**

**NCOH Consortium Agreement (December 2016)**

netherlands centre for one health

# Strategic Research Agenda

## SUMMARY

2016-II

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Leids Universitair Medisch Centrum · Universiteit Utrecht · UMC Utrecht · Wageningen University & Research · Universiteit Leiden · Erasmus MC · amc

# Contents

# 1. Purpose and vision of the NCOH

## 1.1 Purpose and vision of the NCOH

Global trends, such as climate change, population growth, urbanisation, deforestation, increased demand for food, and the strong increase in international trade and travel pose grand challenges to society as a whole. These challenges have in common that they pose serious risks to human, animal, and ecosystem health.

Adequately meeting these challenges should, therefore, involve the development and implementation of durable interventions that emanate from an integrated and balanced perspective in which human, veterinary, wildlife, and environmental elements and considerations are integrated. Research adopting such an integrated perspective is called "One Health research".

The Netherlands harbours world-leading academic research groups across different institutions that are active in various complementary fields of One Health research. These groups have initiated the Netherlands Centre for One Health (NCOH): a science-driven virtual institution, open for participation by *Dutch Universities, University Medical Centers, NWO and KNAW institutes, and TNO and DLO institutes*.

*The vision of the NCOH is to become an internationally-renowned research institute that performs excellent scientific research and education in pursuit of durable solutions to societal challenges requiring a One Health approach.*

The NCOH will fulfil the following purposes:

a. *Functioning as the national coordinating platform for One Health research, performing collaborative fundamental, translational, and applied scientific research that integrates human, veterinary, and environmental elements and considerations (Figure 1).*

b. *Strengthening and consolidating the One Health knowledge and research basis in the Netherlands:* The NCOH should strengthen and consolidate a solid One Health knowledge and research basis in the Netherlands that guides international best practice on addressing grand challenges from a One Health perspective, holding to its core values of high level excellent, solution-driven research.

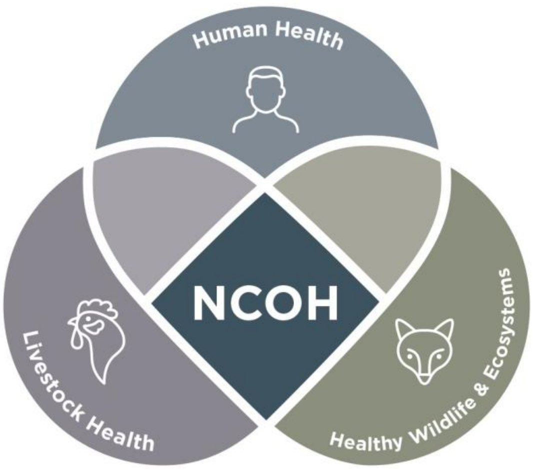

**Figure 1. The One Health perspective**

c. *Providing a trusted and excellent launching platform for public-private partnerships in One Health research:* the NCOH provides a coherent and excellent academic research platform for the initiation and implementation of public-private partnerships in research and innovations of relevance to the NCOH SRA and its Strategic Research Themes, in support of creating sustainable societal and economic impact;

2. *International positioning:* the NCOH is a national centre for One Health research of international stature, contributing to positioning the Netherlands as a guiding country (the Dutch approach) in One Health research. In this role, the NCOH also aspires to take a central and catalysing role in the envisaged European collaboration on One Health research (e.g. the European Joint Programme One Health and Article 185 of the Treaty on the Functioning of the European Union).

# 2. Strategic Research Themes and Solution Sets

## 2.1 The four NCOH Strategic Research Themes

*In pursuit of its vision and purpose, the NCOH focuses its research on four complementary Strategic Research Themes, that combined constitute the long term strategic research scope of the NCOH:*

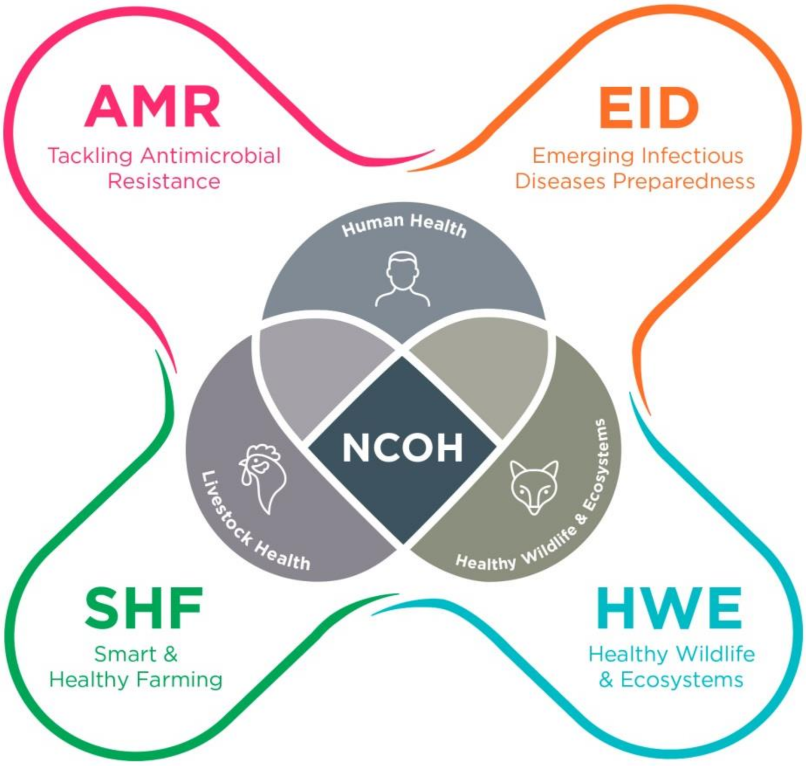


**Figure 2. The four Strategic Research Themes of the NCOH.**

The four Strategic Research Themes share a focus on Infectious Diseases, while recognising that other linked problems affecting human, veterinary, and environmental health, such as pollution (e.g. emissions, toxins, smell, and scenery) and other societal effects, should also be taken into account. The Netherlands harbours some of the world's leading research groups active in these four Strategic Research Themes. This combination makes the Netherlands an ideal environment for One Health research and perfectly positioned to take a leading international role in One Health research focused on infectious diseases.

Antimicrobial resistance and emerging infectious diseases both constitute major global challenges to human health. As such, they constitute the two Strategic Research Themes Tackling Antimicrobial

Resistance and Emerging Infectious Disease Preparedness that predominantly, but not exclusively, focus on human health. Yet, their causes and possible solutions also include multiple components of healthy farming and healthy wildlife and ecosystems. Moreover, both antimicrobial resistance (AMR) and (re-) emerging infectious diseases (EID) also pose huge risks to animal health. Therefore, considering that the Netherlands has one of the worlds' highest farming densities and is one of Europe's main transportation and trade gateways, our country is particularly vulnerable to these challenges. This supports including Smart and Healthy Farming and Healthy Wildlife and Ecosystems as two Strategic Research Themes in their own right within the NCOH-SRA.

### 2.1.1 NCOH Strategic Research Theme: Tackling Antimicrobial Resistance (NCOH-AMR)

The NCOH-AMR addresses the following challenge:

*To decrease the morbidity and mortality of antibiotic-resistant bacterial infections in humans, through use-inspired One Health research on AMR.*

The global emergence of antibiotic resistance, coupled to the increasing complexity of medical care relying on effective prevention and treatment options for bacterial infections, poses a serious challenge for modern medicine in the developed world. The success of antibiotics in the treatment and prevention of bacterial infections is now rapidly leading to their downfall. Exposing bacteria in humans and animals for decades to these ‘wonder drugs’ has augmented the emergence of resistance against all available antibiotics through selection of resistant mutants and cross-species transmission of bacteria, plasmids and resistance genes. Spill of human and animal waste also contaminates environmental niches maintaining continuous exposure of humans and animals (for some examples see Box 1). Better understanding the dynamics of these events, followed by effective interventions, is one of the cornerstones towards a sustainable solution for this global challenge.

**Box 1.** In 2012, there were about 450 000 new cases of multidrug-resistant tuberculosis worldwide. According to the European Antibiotics Resistance Surveillance network (EARS0NET) of the European Centre for Disease Prevention and Control more than one third of *Klebsiella pneumoniae* isolates and more than one half of *Escherichia coli* isolates from invasive infection in hospitals were resistant to at least one antimicrobial group under surveillance in 2013. The proportions of extended-spectrum β-lactamase-producing *E. coli* and *K. pneumoniae* from invasive infections are rapidly increasing in Europe.

Also carbapenemase-producing *K. pneumoniae* have emerged in Europe and are currently endemic in hospitals in the Mediterranean region, posing a threat for introduction in Dutch health care settings. The EU average of ampicillin resistance among *Enterococcus faecium* is 88%, while, on average, 8% of *E. faecium* in EARS-NET are both resistant to ampicillin and vancomycin.

For *Staphylococcus aureus*, 18% (EU average) of isolates was resistant to methicillin in 2013. Studies of the ECDC have estimated that the total number of annual deaths due to infections caused by drug-resistant bacteria in Europe alone was 25 000 and that the associated costs amounted to 1.5 billion euros per year. In a recent review, a continued rise in resistance by 2050 is estimated to lead to 10 million deaths every year worldwide and an increase of 2% to 3.5% in gross domestic product , costing the world up to 100 trillion USD.

In the Netherlands we have succeeded in maintaining low levels of antibiotic resistance in human disease, despite high antibiotic use and high prevalence of antibiotic resistance in agricultural reservoirs. Yet, the global increase of resistance will inevitably also affect our country and given the density of animals and humans the Netherlands represents an ideal setting for rapid spread of AMR. If we fail to effectively respond to this threat, an increasing number of bacterial infections will become untreatable**.**

Building on a strong scientific track record and well-established research infrastructures, the NCOH-AMR brings together Dutch leading research groups from complementary disciplines that will structurally collaborate in excellent research aimed at developing durable solutions that meet this challenge.

### 2.1.2 NCOH Strategic Research Theme: Emerging Infectious Diseases Preparedness (NCOH-EID)

NCOH-EID brings together Dutch top scientists on emerging infectious diseases (EID) under one virtual roof with a common strategic research agenda addressing the following challenge:

*To improve preparedness for (re-) emerging infectious disease outbreaks by developing improved EID prediction, detection, and prevention and control strategies in a time frame that is compatible with fast-spreading EID, based on fundamental research insights into host, microbial, and environmental factors leading to disease (re-) emergence.*

The past decades witnessed the emergence of novel infectious diseases and changing patterns in existing diseases across the globe with substantial impact on humans and animals, as well as the economy (for some examples see Box 2).

**Box 2:** Notable examples of (re-)emerging infectious diseases are the incursions into Europe of avian influenza H5N1, H7N9 and H5N8, Bluetongue virus, and Schmallenberg virus, with major impact on the animal sector, and the human disease outbreaks following cross-species jumps of zoonotic pathogens, for instance the SARS, MERS, and Ebola virus. The economic losses caused by the SARS CoV outbreak, that affected 8000 persons of which 10% died, has been estimated to amount to tens of billions of US Dollars, primarily due to travel restrictions, effects on tourism and trade. Similarly, the Ebola outbreak has almost completely paralyzed the already weak health systems in the three affected countries, and led to the death of an estimated 9% of the total medical workforce. Moreover, it triggered massive global response, with high costs to hospitals and public health systems preparing for potential travel associated cases or ill healthcare workers. Avian influenza emergence in China led to a 25% drop in the income of the Kentucky fried chicken chain, despite clear public health messages that the risk to consumers was negligible. While these are seemingly exotic examples, EID outbreaks closer to home are also possible, with the recent examples of Q-fever, the increasing prevalence of hepatitis E human cases for which main modes of transmission to humans remain to be determined, and the presence of swine influenza from which the pandemic influenza H1N1 in 2009 emerged. The Netherlands experienced the largest Q fever outbreak between 2007 and 2010 ever reported, involving more than 4000 human cases. Epidemiological and molecular analysis revealed dairy goats at the source of the outbreak. Control measures focusing on dairy goats resulted in a decrease of human cases and the ending of the outbreak.

While these emerging diseases compared to some endemic global infectious diseases have remained relatively limited in terms of morbidity and mortality, a huge challenge is the uncertainty of the potential for spread among humans, known as pandemic threat. The H5N1 and H7N9 influenza viruses, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronaviruses and Ebola virus cause severe, often fatal illness in humans, and it remains unclear what determines their transmissibility, although few mutations may suffice to acquire that property. As a consequence, despite the limited size of the outbreaks, impact on the society and economy of affected countries has been very severe. Therefore, the World Health Organization has called for development of an R&D blueprint for the most serious pandemic threats, including the development of smarter detection systems, a roadmap to development of novel treatments and interventions, and the clinical research capacity to evaluate these in the face of an epidemic. This blueprint will be presented at the world health assembly in 2016. The list of priority pathogens has been published (http://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/)

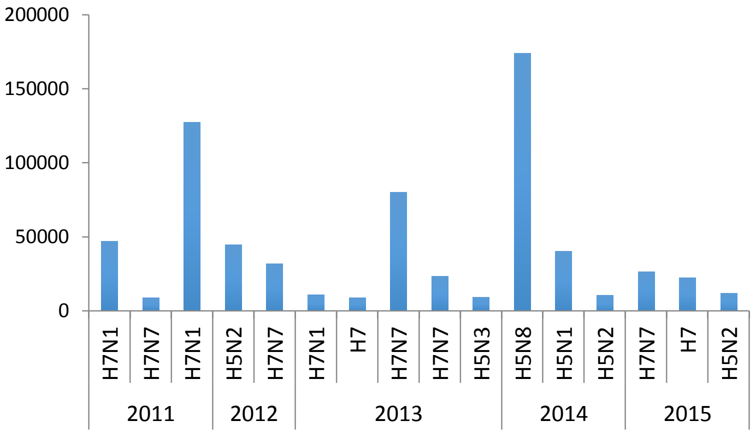


**Figure 3. Number of poultry culled per year for infection with influenza viruses of subtypes H5 and H7** (source: WAHID, OIE)

Similar issues apply in the veterinary field. A single outbreak of an EID can trigger enormous economic losses from culling, transport restrictions, trade bans and other consequences of disease outbreaks and control activities. The high density and increasing size of livestock farms in The Netherlands and elsewhere create new challenges in disease prevention and control, as was evident during the H7N7 avian influenza outbreak, and also the Q fever problem. Influenza viruses with surface hemaglutinins of subtypes H5 and H7 are a special concern due to their propensity to acquire changes that may result in devastating poultry outbreaks with zoonotic potential. Outbreaks detected through mandatory surveillance are solved by immediate culling of the animals on the farms. Unfortunately, despite high levels of biosecurity, such events occur quite regularly (Figure 3). The most recent unprecedented global spread of H5N8 influenza viruses through wild birds, leading to almost simultaneous poultry outbreaks in Germany, The Netherlands, the UK and the US served as another warning of how small the world has become.

The emergence of specific vector borne bacteria or arboviruses (viruses spread by arthropod vectors such as mosquitos, midges, or ticks) in parts of Europe – even if few cases occur – immediately raises questions about the safety of the blood supply, limiting availability of blood and blood products or leading to costly screening programs. In the veterinary world, the Schmallenberg virus epidemic should serve as a warning: this previously unknown virus spread with unprecedented speed. Although it presented with initial mild clinical symptoms in cattle and sheep in a small geographical area, major complications became evident months later with severely malformed new-born calves and lambs. Understanding vector ecology is an important aspect as well, illustrated by the lessons learned in Italy, where a large outbreak of Chikungunya virus infection from an infected traveller was possible because the mosquitos competent for transmission of this virus had emerged over the past years.

## Re-emergence of bacterial zoonoses

Contrary to the emergence of zoonotic virus infections most zoonotic bacterial infections are endemic and can re-emerge from this endemic state. Q fever is the most recent eye-catching example in the Netherlands. To control the human outbreak involving more than 4000 human cases, nearly 60.000 dairy goats were culled and over 800.000 animals were vaccinated between 2008 and 2011. Chlamydiosis shows much similarity to Q fever, but its disease burden and prevalence is unknown due to poor diagnostic performance of the available tests. A better understanding of Chlamydiosis might prevent human disease. *Streptococcus suis* is one of the most important pathogens in pigs and also causes disease in humans through zoonotic transmission. While perceived as a rare zoonotic disease in the Netherlands, *S. suis* is the most common cause of bacterial meningitis in adults in several regions in Southeast Asia and China. Finally, Tuberculosis and brucellosis are chronic zoonotic bacterial infections which are currently rare in humans in Western Europe but still endemic in farm animals and wild-life populations in several European countries. Countries like the UK and Ireland are still facing an ongoing bovine TB outbreak and in other nearby EU member states (Spain, France and Germany) animal tuberculosis and brucellosis are currently considered re-emerging diseases potentially threatening both veterinary and public health.

## Drivers for emergence

Systematic analysis of outbreaks, as exemplified in Box 2, and changing patterns of disease have identified important drivers for their emergence, often resulting from a complex interplay between humans, animals, and their environment. The past outbreaks have shown that the Netherlands harbours tremendous expertise in rapid response to EID events and supporting outbreak investigations, but that evidence-based intervention measures typically are too late to impact on the ongoing outbreak. This is not different from the internationally-occurring high-impact outbreaks of SARS, MERS, H5N1, and Ebola and has led to a call for integrated preparedness research. Targeted efforts are needed to detect new diseases timely, to identify critical knowledge gaps, pre-emptively or as fast as possible during outbreaks, and to design and evaluate control, prevention, and intervention strategies. These challenges are the focus of the NCOH-EID program.

### 2.1.3 NCOH Strategic Research Theme: Smart and Healthy Farming (NCOH-SHF)

NCOH-SHF addresses the following challenge:

*To reduce or eliminate human health risks arising from livestock and food production through research contributing to more healthy animals, early signalling of animal health parameters, and smart and healthy farming practices.*

Animal husbandry and animal products are important to fulfil the global demand for high-quality food, and remain an important commodity despite occasional outbreaks. Livestock production is currently facing enormous challenges, not only related to animal disease threats, but also to the fact that the license to produce is under debate due to risks to public health and sub-optimal animal welfare, as well as environmental degradation. Socio-economic demands for healthy livestock production chains emphasize that animals should be kept under conditions that (i) optimize animal health and prevent development of disease and health problems (without systematic use of antibiotics), (ii) minimize the influence on the environment, and (iii) provide an end-product that is safe for the consumer.

Public health risks associated with livestock production and processing either occur through:

- Direct occupational health risks in livestock production and processing;
- Contamination in stages of the food chain, either directly (meat) or indirectly, through contact with environmental contamination; a well-recognized global health threat is the potential transmission of pathogens through the food chain. These can be animal pathogens, but also combinations of human and animal pathogens for instance when food is contaminated from environmental sources, resulting in exposure of humans to multiple pathogens simultaneously with unforeseeable consequences. A recently completed World Health Organization burden of disease study[1] estimated the burden of foodborne disease to be similar to that of major infectious diseases (human immunodeficiency virus-acquired immune deficiency syndrome, malaria and tuberculosis). This points at major vulnerabilities of the food chain, and these come to light with every emerging disease outbreak.
- Exposure of individuals, living in the immediate surroundings of livestock producing units, to emissions of (infectious) microbial agents, their toxins or other (non-infectious) particles and waste streams (manure) containing (infectious) microbial agents.

A complicating factor for livestock production in the Netherlands is that livestock production takes place in a densely populated country creating ample opportunities for pathogen exchange between humans and animals. The livestock production sector is therefore continuously looking for ways to safeguard and improve the health of animals from birth to delivery to the slaughterhouses as well as safe food products from farm to fork. This as a way to improve animal health and sustainable production thereby reducing the potential public health effects and potentially through manure production and

[1] *Havelaar et al; PLoS Med. 2015 Dec 3;12(12):e1001923.*

management. Reduction of environmental emissions is in its infancy and has received limited attention, despite continuous intensification of production over recent decades. In addition, the increasing size and density of farming provides a challenge to prevention of devastating animal disease outbreaks in itself, indirectly also affecting human health given its potential impact on food production.

The demand for healthy animals and food products requires sufficient expertise, knowledge development and innovation in the area of healthy livestock production, areas in which knowledge is still sorely lacking. Multidisciplinary solutions and innovations are vital for developing and realising healthy livestock production. Effective solutions are complex and should not move risks from one reservoir (food, environment or work environment) to another. For healthy livestock production it is important to acknowledge and utilize the contribution and cooperation between the chain partners in the production process. Complex interactions between farming systems, pathogens and their toxins, and the animals all affect healthy livestock production in a healthy environment. Within NCOH, all fields of expertise are present to ensure an integral approach to tackle current challenges. Through NCOH, research can be conducted, knowledge can be generated and processes can be guided in every aspect and at every juncture of healthy livestock production.

### 2.1.4 NCOH Strategic Research Theme: Healthy Wildlife- and Ecosystems (NCOH-HWE)

The NCOH-HWE addresses the following challenge:

*To decrease the detrimental effects of wildlife-related disease on human health, livestock production systems and ecosystems through understanding, anticipation, and (potential) prevention of environmental factors driving spread of wildlife diseases using an integrated, multidisciplinary approach.*

**Box 3:** More than 70% of emerging zoonoses in humans have a wildlife source (Jones et al., Nature 451, 2008). Globally, the outbreaks of diseases such as Ebola and West Nile fever, have called attention to zoonotic diseases and the magnitude of their impacts on human health and national economies.

Wildlife species are also involved in transmission of disease to and from livestock and other domestic animals, resulting in major animal health welfare problems and economic losses. African swine fever has already cost the Russian economy around US$1 billion and expenses due to bovine tuberculosis in England surpassed € 100 million in 2010/2011.

Wildlife diseases are clearly an ecological force in shaping wild populations, communities and ecosystems as demonstrated by the spread of rinderpest across Africa followed by its global eradication. In some circumstances, wildlife diseases may threaten biodiversity and push endangered species to the brink of extinction. Examples are canine distemper in black-footed ferrets, chytridiomycosis in frogs, avian pox in endemic Hawaiian birds, and tuberculosis in free roaming and captive wildlife populations. There is a paucity of evidence-based best management practices in dealing with wildlife disease in ecosystems.
Vectors have an important role in indirect transmission of pathogens amongst wildlife, domestic animals and humans. Current global changes in weather conditions and habitat structure are affecting vector occurrence and competence, with concomitant changes on disease occurrence.

The Netherlands forms a closely interwoven patchwork of urban, agricultural and natural areas and boasts both a high diversity and number of wild animals. This recently led an international team of wildlife health experts to conclude that “the socio-economic spheres of animal agriculture and trade, food safety, human health and nature conservation ... are large in the Netherlands, as its national vulnerability to the negative impacts of infectious diseases due to an exceptionally high density of people, livestock and wildlife”. Based on detailed review of past outbreaks, a large proportion of (re-) emerging infectious diseases in both humans (e.g. tularaemia, Lyme disease) and farm animals (e.g. avian influenza, African swine fever) have their origin in wildlife. Some species of wildlife, such as gulls and pigeons, may be important as carriers of antibiotic-resistant bacteria due to exposure to human and farm animal waste. Wildlife also interact directly with farm animals, especially those that graze on pastures and those that are housed in open-range farms (e.g. poultry, pigs). Therefore, NCOH-HWE closely connects to the other NCOH Strategic Research Themes.

Globalisation in all its aspects—including human travel, livestock trade, intensification of livestock production, loss of natural habitat, and climate change—is changing the nature and scale of wildlife-related diseases. In turn, this is affecting the structure and health of ecosystems. However, the understanding of the exact mechanisms that drive the occurrence and spread of wildlife-related diseases is insufficient to successfully mitigate negative effects. Furthermore, it is difficult to measure and monitor diseases in wildlife. Finally, the understanding of long-term effects of wildlife-related diseases in a changing environment is insufficient to implement timely preventive strategies.

The NCOH-HWE aims to limit the detrimental effects of wildlife-related diseases by focussing on analysis of the effects of the evolving environmental factors, such as habitat (e.g. through changing water levels), ecosystem structure (e.g. changes in host species composition) and of weather conditions (global warming) on the occurrence and spread of wildlife disease, and on the assessment of mitigation measures. This will be addressed via a multi-disciplinary One Health approach involving close collaborations between top research institutes and universities at national and international levels.

## 2.2 The NCOH Solution Sets

Scientific in its core, the NCOH is a solution-driven initiative, acknowledging that there is not one solution to the challenges addressed by the NCOH. Across the four Strategic Research Themes, the NCOH has therefore formulated a set of complementary Solution Sets (Figure 4) that combined provide for the long term research focus on the NCOH in any of its four Strategic Research Themes.

*A Solution Set is a combination of research projects that, individually or collectively, is geared towards the (long-term) development of solutions (knowledge, processes, strategies, recommendations, tools, products) to the key challenges targeted by the NCOH in any of the four Strategic Research Themes.*

Not all Solution Sets are covered by each of the four Strategic Research Themes. Some, such as New Antibiotics and Outbreak Control Strategies, are specific to a single Strategic Research Theme. However, the majority of the Solution Sets provide for a common grouping of highly interconnected research topics across two or more of the NCOH Strategic Research Themes, allowing for the highly needed interaction across the Strategic Research Themes.

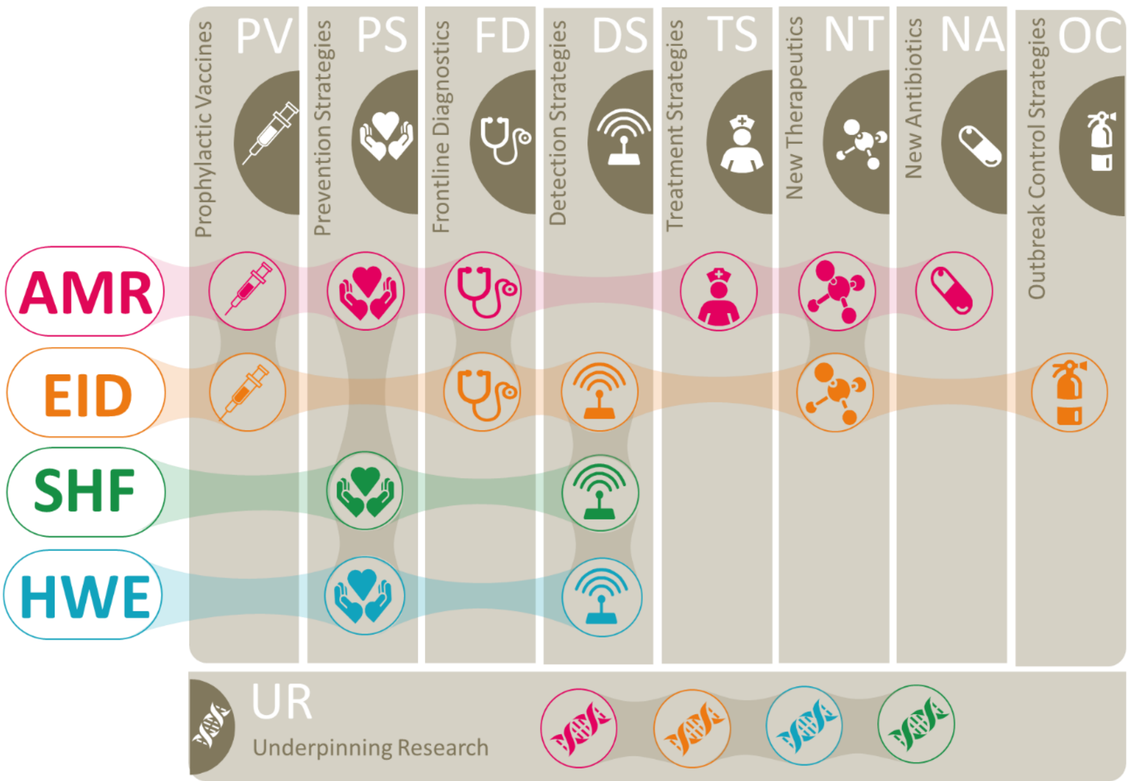


**Figure 4. The NCOH Solution Sets.**

Within each Strategic Research Theme, Research Projects are defined and implemented in the most relevant and urgent Solution Sets for that particular Strategic Research Theme. A Research Project (RP) is a project that is formally adopted as part of the NCOH Strategic Research Agenda and that fits within any of the four Strategic Research Themes, and – within the Strategic Research Theme – in any of the Solution Sets that comprise the research focus of that Theme. RPs in a Solution Set may be grouped into a Research Track.*

At any given point in time, the NCOH research portfolio therefore comprises a set of RPs across the four Strategic Themes ranging from fundamental exploratory research to applied RPs and covering the Solution Sets of the NCOH (see Figure 5).

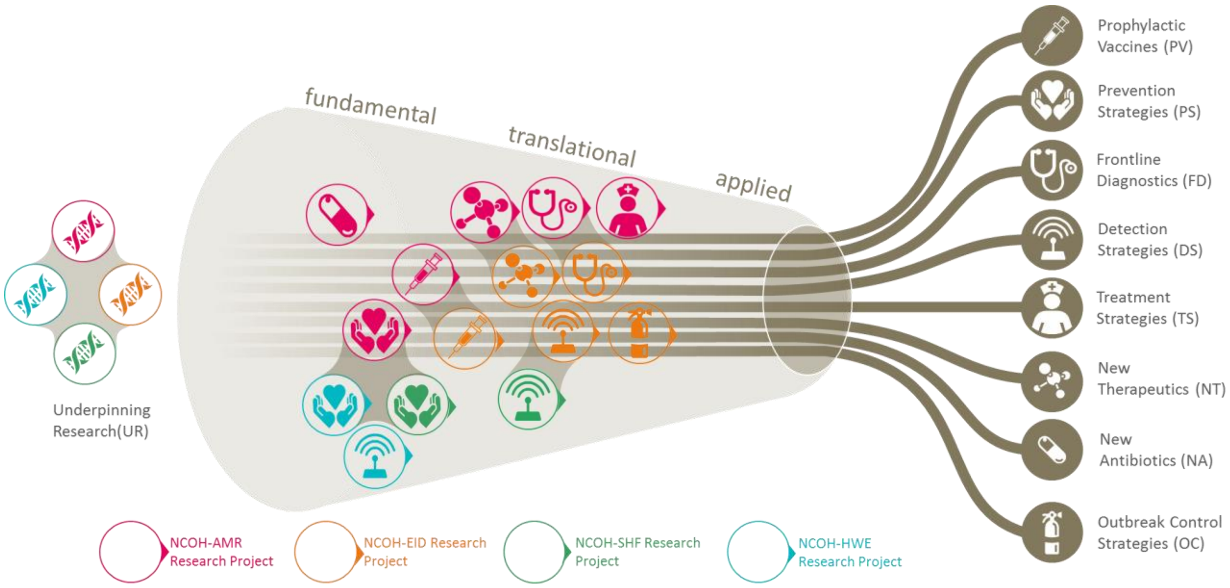


**Figure 5. NCOH Research Projects.** The NCOH RPs span from fundamental research to applied research in clinical studies and other pilot projects (number, type and location of RPs are indicative.)

RPs located at the far left side of this range, given their intrinsic fundamental character, may be less pronounced in their fit within a specific Solution Set than RPs that have already progressed along the funnel (e.g. an novel therapeutic evaluated in Phase I studies).

# 3 Research Project Portfolio of NCOH-AMR

## 3.1 Introduction of the NCOH-AMR research agenda

The goal of the NCOH-AMR is to decrease the morbidity and mortality of bacterial infections in humans, through use-inspired, excellent, fundamental, translational, and applied One-Health research on AMR. The NCOH-AMR will pursue this goal through a combination of complementary Solution Sets that intervene at three levels of the problem-chain of AMR (see Figure 6). Together these Solution Sets comprise the long-term research focus of the NCOH-AMR.

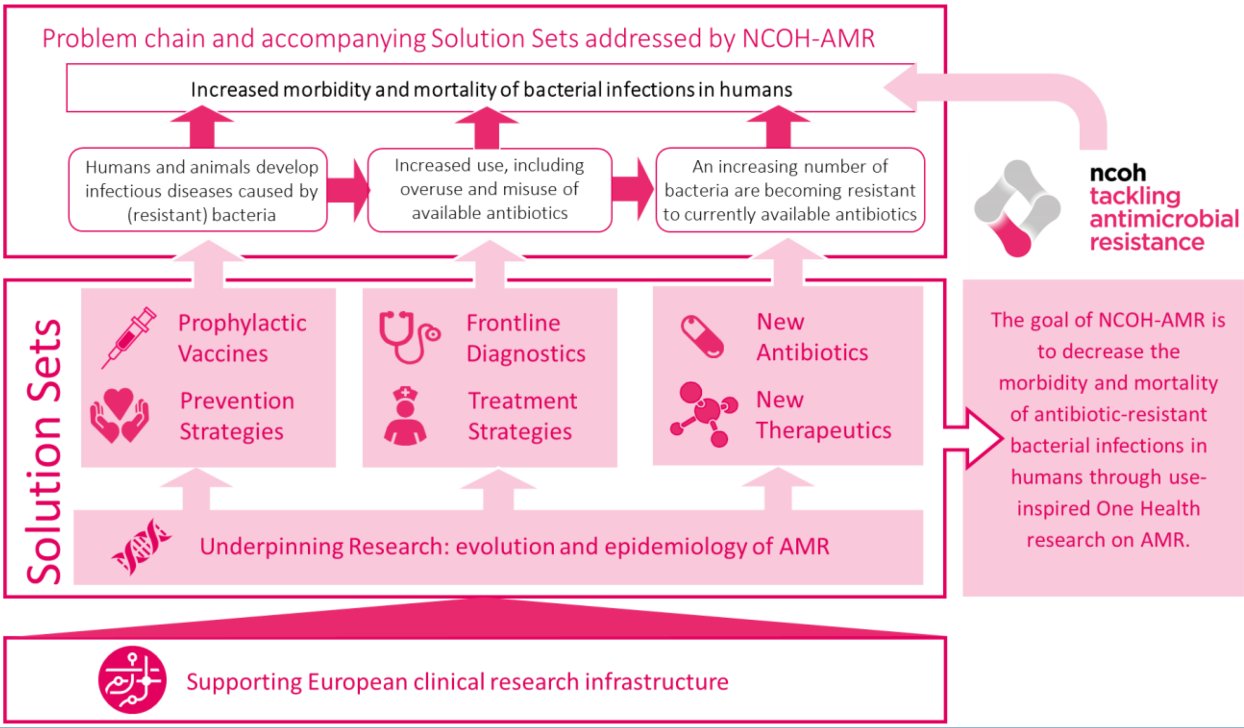


**Figure 6. Solution Sets of NCOH-AMR.**

1. Prevention of bacterial infections: addressing the root causes of the rising problem of antibiotic resistance, the NCOH-AMR will focus its research efforts on two Solution Sets in pursuit of preventing bacterial infections in humans and animals: *Prophylactic Vaccines* and *Prevention Strategies*;

2. Antibiotic stewardship: Contributing to decreasing the (mis)use of available antibiotics, the NCOH-AMR will invest in two Solution Sets that support antibiotic stewardship in humans and animals, which includes optimizing treatment through pharmacokinetic and pharmacodynamic priniciples: *Frontline Diagnostics* and *Treatment Strategies*;

3. Treatment of bacterial infections: in pursuit of decreasing our dependency on the diminishing number of effective antibiotics, the NCOH-AMR research portfolio will include research on two complementary Solution Sets for humans and animals: *New Antibiotics* and *New Therapeutics*.

The NCOH-AMR will also include underpinning research, supportive to the other NCOH-AMR Solution Sets, on the *Epidemiology, evolution and dynamics of antibiotic resistance* in humans, animals and the environment and the migration of bacteria, plasmids and resistance genes between these ecological niches.

### 3.2 NCOH-AMR: Prophylactic Vaccines (PV)

Vaccines have been instrumental in reducing of the societal burden caused by infectious diseases. Both human and animal vaccines against several bacteria effectively prevent and contain infectious disease outbreaks (e.g. pertussis, bacterial meningitis). Conjugate vaccines have reduced the total incidence of pneumococcal infections in children with more than 80%, and at the same reduced the incidence of vaccine serotypes in unvaccinated elderly, through indirect protection, with 90%. We recently demonstrated that the 13-valent pneumococcal vaccine reduced – in healthy elderly - the incidence of vaccine-type community-acquired pneumonia and invasive pneumococcal disease with 45% and 75%, respectively[2]. This study provides the proof-of-concept for the development of new vaccines against a wide range of bacterial infections in adults that could constitute a durable solution for the problem of AMR. Currently, this Solution Set contains two tracks on prophylactic vaccine development: (i) pathogen specific vaccine development focusing on *Staphylococcus aureus*, *K. pneumonia* and *E. coli* and (ii) alternative animal models for vaccine evaluation to provide insight into *Staphylococcus aureus* pathogenesis in an in vivo model without limitations of host restriction. In case of vaccination, some the currently available infection and vaccine models are not suited for the pathogens we have defined to examine in this Solution Set.

### 3.3 NCOH-AMR: Prevention Strategies (PS)

Continued efforts are needed in the development and implementation of infection prevention strategies that will be translated into evidence-based protocols and guidelines. Especially for hospital-acquired bacterial infections (e.g. methicillin-resistant *S. aureus* (MRSA), ESBL/CP-producing bacteria, vancomycin-resistant enterococci), infection prevention measures are important tools in preventing hospital outbreaks of resistant bacteria. Furthermore, more efficient preventive strategies are needed in high-risk populations, such as critically ill patients, transplant recipients and otherwise immunocompromised subjects, to improve patient outcome and to reduce antibiotic use. For controversial approaches, such as using topical antibiotics to prevent infections in the intensive care unit[3,4] or after surgery[5], the ecological risks for selecting resistance must be balanced against the benefits for patients and society (in terms of costs). As for treatment strategies, large-scale well-designed clinical studies are needed to quantify the effects of prevention strategies.

[2] *Bonten et al., N Engl J Med, 2015, 372(12):1114.*
[3] *de Smet et al. , N Engl J Med, 2009 ,360(1):20-31.*
[4] *Oostdijk et al., JAMA, 2014, 312(14):1429-37.*
[5] *Bode et al., N Engl J Med, 2010, 362(1):9-17*

## 3.4 NCOH-AMR: Frontline Diagnostics (FD)

Many infections are treated empirically, i.e., without identification of the causative pathogen. Moreover, in many cases the causative pathogen of infection remains unidentified, leading to unnecessary as well as inappropriate antibiotic use. For instance, it is estimated that about 70% of community-acquired respiratory infections in humans are of viral origin. Most of these infections can be treated safely without antibiotics, especially in ambulatory patients. Yet, a 'better safe than sorry' attitude of many physicians in combination with patient pressure leads to frequent antibiotic prescriptions. In hospitals, physicians increasingly treat infected patients with last resort antibiotics in anticipation of an antibiotic-resistant pathogen, as susceptibility results will only be available after at least 24 hours (and usually more). Diagnostics that rapidly (at the point of care) provide reliable results, at low costs, are needed to counteract these practices.

## 3.5 NCOH-AMR: Treatment Strategies (TS)

Unnecessary use of broad-spectrum treatment strategies is another aspect of inappropriate antibiotic use. For instance, based on retrospective analyses it has been proposed that patients with community-acquired pneumonia should be treated with a combination of a β-lactam and a macrolide antibiotic, or otherwise with a new fluoroquinolone, instead of β-lactam monotherapy. Both the combination therapy and the new fluoroquinolone augment the antibiotic spectrum, thereby increasing the selective pressure for antibiotic resistance. We recently demonstrated the non-inferiority of the "narrow-spectrum approach"[6] and more well-designed clinical studies are needed to change guideline recommendations, currently favouring broad-spectrum approaches. Similarly, current guidelines for empirical treatment of sepsis include the use of broad-spectrum combination therapy or of carbapenemase antibiotics to cover ESBL-producing bacteria, based on poorly evaluated risk factors. The positive predictive values of these risk factors appeared <10% in the Dutch hospitals, implying that guideline adherence will stimulate unnecessary use of these antibiotics[7].

## 3.6 NCOH-AMR: New Antibiotics (NA)

Up to the 70's of the 20th century, novel (classes) of antibiotics became available for human and animal health care at regular intervals. However, in the last four decades only 5 new antibiotics acquired market authorization for treatment of infections in humans. With the obvious discrepancy between a rapid emergence of AMR and an (almost) completely halted pipeline of new classes of antibiotics in the final stages of development, our antibiotic arsenal is rapidly decreasing, and physicians are becoming more and more dependent on a decreasing number of effective 'last resort' antibiotics. By introducing novel classes of antibiotics, to which

[6] *Postma et al, N Engl J Med, 2015, 372(14):1312.*
[7] *Rottier et al., Clin Infect Dis, 2015, pii:civ121.*

resistance in bacteria has not been reported, we can decrease our dependency on the existing antibiotics.

## 3.7 NCOH-AMR: New Therapeutics (NT)

A complementary strategy to the development of new antibiotics is the development of alternative therapeutic modalities, that can either eliminate bacteria without selecting for novel resistance traits, or that modulate the immune response of the host during (or before) infection. Such strategies should be based on mechanisms of action not yet used by existing antibiotics or whose delivery mechanisms are not (or at least less) susceptible to evolutionary resistance pressure, or on better understanding of the innate and humoral immune response to bacterial infections caused by species creating current and future treatment problems because of AMR.

## 3.8 NCOH-AMR: Underpinning Research (UR): Drivers of Emergence and Spread

The overall objective of this part of the research agenda of the NCOH-AMR is to provide a better insight in the epidemiology and evolution of AMR, specifically the effect of antimicrobial usage on antimicrobial resistance. Use will be made of molecular techniques, bioinformatics, and large clinical studies that enable to understand the dynamics and population structures of antimicrobial resistance.

## 3.9 NCOH-AMR Clinical research infrastructure

NCOH-AMR contains the necessary infrastructure to design and execute observational and experimental studies across the whole spectrum of patient populations affected by AMR. Research Projects in NCOH-AMR will make use – where relevant – of the European clinical research network as established ***in Combatting Bacterial Resistance in Europe (COMBACTE).*** As part of the New Drugs for Bad Bugs program from the Innovative Medicine Initiative , UMC Utrecht acts as the managing entity of three topics (COMBACTE, COMBACTE-CARE and COMBACTE-MAGNET). Together with >40 academic partners in Europe a high-quality clinical trial network is built in Europe. Within this network (for which the EORTCC serves as an example) studies related to new treatment options for MDR bacteria will be performed. The data management and clinical trial infrastructure created within COMBACTE is also available for multi-centre studies within the Netherlands in the field of AMR, as part of the Stichting Infectieziekten Onderzoek Nederland, a collaboration between academic and non-academic hospitals in the Netherlands that started in 2015.

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# 4. Research Project Portfolio of NCOH-EID

## 4.1 Introduction to the NCOH-EID Strategic Research Agenda

The goal of the NCOH-EID is to improve research and (veterinary and public health) preparedness for emerging and re-emerging infectious diseases. It will do so by providing fundamental insights into host, microbial, and environmental factors leading to disease (re-)emergence and to translate this knowledge into improved prediction, detection, prevention, and control strategies in a time frame that is compatible with fast-spreading emerging infectious diseases. The NCOH-EID research will encompass the following Solution Sets (see Figure 7) that together comprise the long-term research focus of the NCOH-EID. There are several research projects within the EID Solution Sets that cut-across other themes, particularly NCOH-SHF and WEH, and the intention is to develop joint programs for topics with complementary focus. Where such links are foreseen, they are indicated in the text.

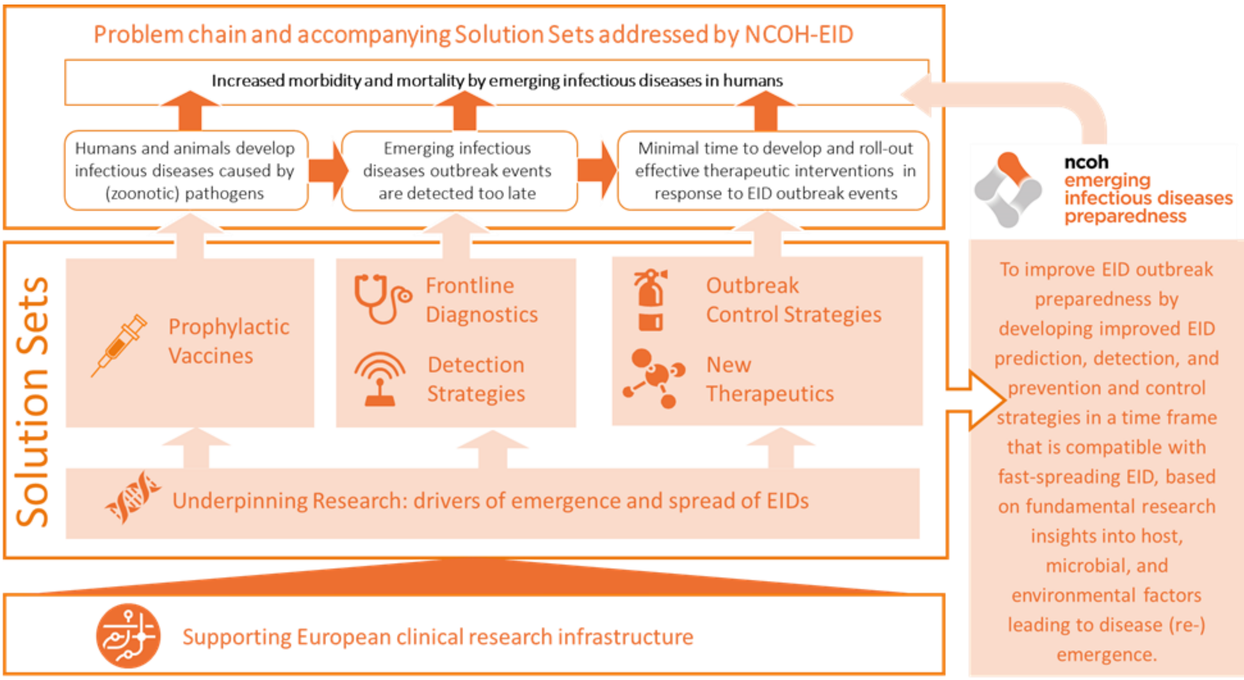


**Figure 7. Solution Sets of the NCOH-EID.**

1. Prevention of EIDs: Effective and cheap vaccines and accompanying vaccination strategies are a crucial element in EID prevention and preparedness. The NCOH-EID research agenda will therefore include innovative research on human and animal *Prophylactic Vaccines.*

2. Early Detection: Lessons from the recent past (Q-fever, Ebola) learn that early identification of bacterial and viral infections is critical to contain outbreaks of emerging infections. Two complementary Solution Sets: *Frontline Diagnostics* and *Improved Detection Strategies* are therefore form the second part of the NCOH-EID research agenda;

3. Control of EIDs: In the event of an EID outbreak, the window of opportunity to control the outbreak is short. Novel therapeutics (e.g. broadly-active antivirals) can be a valuable asset in the outbreak control. Moreover, understanding the key properties of an EID is crucial to gauge the human and veterinary public health response and to come up with proportionate, effective, and acceptable control measures in case of unexpected EID outbreaks. The NCOH-EID has therefore included research in the Solution Sets *New Therapeutics* and *Outbreak Control Strategies.* The NCOH-EID will also include underpinning research, supportive to the other NCOH-EID Solution Sets, on the *Drivers of emergence and spread of EIDs.*

## 4.2 NCOH-EID: Prophylactic and Post-exposure Vaccines (PV)

Collaboration between veterinary and human health - academically, governmentally, and industrially - is extremely important for the control of infectious diseases. In-depth knowledge on antigenic make-up of pathogens, the host response to these antigens, specific approaches to modifying this response through species-specific adjuvants, and vaccine delivery are needed for development of effective vaccines. A specific target in zoonotic infections is the possibility to not only reduce disease in the reservoir hosts – if it exists – but also to reduce pathogen circulation in the reservoir host, which may be a challenge and for instance require vaccines that develop strong mucosal immunity. Ideally, vaccines are needed that induce an immune-response that can be distinguished for the response to wild-type infection. While vaccination of animals for prevention of human disease may seem a straightforward approach, acceptance of such vaccines is likely to be low if animals appear healthy (MERS Coronavirus, hepatitis E, Chlamydia etc.) unless delivery is low cost and simple. Development of vaccines requires investment in the entire chain from protective antigen discovery, vaccine production, vaccine delivery to efficacy studies requiring basic knowledge about immunity. All expertise required for the needed multidisciplinary molecular-to-population vaccine research approach is available within NCOH-EID.

## 4.3 NCOH-EID: Frontline Diagnostics (FD)

The unpredictable nature of EID makes diagnostic preparedness challenging, as the clinical presentation of most EID do not differ from common disease syndromes. With the rapid development of molecular diagnostic methods, more generic "catch-all" culture-based or microscopy based techniques have been largely replaced in diagnostic virology, and this trend is expected to persist in the coming years. In addition, the pressures to reduce healthcare costs have impacted on the acceptance of broader diagnostic evaluation of disease syndromes, leading to significant underdiagnoses. The average time to initial laboratory confirmation of outbreaks of EID notified to WHO is a little over one month, but with substantial longer delays in many instances (Chan et al., 2010). Recent outbreaks in The Netherlands show similar timelines: a long delay was seen in the initial discovery of the Q fever outbreak, and the clinical syndrome that was eventually diagnosed as Schmallenberg virus. This also includes diagnosis of unusual clinical syndromes in travellers that can introduce EID[8]. In pursuit of improving our capability for timely detection of EID, the improvement of frontline diagnostic capabilities is therefore essential.

[8] *Cleton et al., 2012 Nov;55(3):191-203.*

## 4.4 NCOH-EID Detection Strategies (DS)

Lessons from the recent past (with Q-fever and Ebola outbreaks) learn that early identification of bacterial and viral infections is critical to contain outbreaks of emerging infections. By default, EID outbreaks are caused by a diverse range of pathogens, for which routine (medical and veterinary) clinical and public health laboratories are not specifically testing. Historically, with the common use of culture-based catch-all methods combined with additional characterization could provide an initial diagnosis or the notion that something unusual was causing the disease. With the rapid transition of (medical and veterinary) clinical and public health laboratories to molecular diagnostic approaches, however, this catch-all approach has been replaced by methods requiring prior knowledge of the targeted pathogen. As the range of EID is large and unpredictable, preparedness calls for novel, generic approaches to disease and pathogen detection, and a collaborative approach to outbreak response.

## 4.5 NCOH-EID: New (alternative) Therapeutics (NT)

A specific challenge with novel EID is that - typically - the field is left empty-handed when trying to treat new viral disease outbreaks. The traditional drug discovery pipeline aiming to develop specific antivirals is long, and little emphasis has been on development of broadly-reactive antiviral drugs, unlikely the AMR field. This gap is increasingly criticized in recent high-profile EID outbreaks and has triggered studies into repurposing of commonly used and registered drugs, rapid development of antibody based treatments, and the search for novel drugs that target components of the pathogen host interaction common to multiple viruses.

## 4.6 NCOH-EID: Outbreak Control Strategies (OC)

The control of zoonotic EID outbreaks depends on the nature of transmission, and the effectiveness of the newly introduced pathogens to spread among humans or animals. With that, the focus of intervention strategies differs: for highly transmissible EID, where outbreaks occur in human populations or animal populations following a single introduction, focus of intervention will be in the host affected by disease, as for instance was the case in Ebola. For EID of zoonotic origin in which continuous zoonotic exposure is a driver of human disease, different approaches are needed. This likely includes development of vaccines to control pathogen circulation in animals, as has been used to control the Q fever outbreak and has been suggested for MERS CoV and avian influenza, for instance. While such vaccines may not be acceptable for routine disease control, emergency vaccination strategies can be an added tool to combat an EID outbreak. This has been one of the strategies in the Castellum project.

## 4.7 NCOH-EID: Underpinning Research on the drivers of Emergence and Spread

Changes over the past decades in population demographics, animal husbandry practices and scale of animal production, and extent and speed of global travel and trade have increased the likelihood of international spread of diseases and vectors, but also affect evolution of pathogens which as a consequence again affects their ability to spread. The mechanisms underlying these changes are complex and multifactorial, and require epidemiological and laboratory analyses to fully understand describe the patterns of disease emergence and spread. Most high impact EIDs have in common that they appear unexpectedly, have great impact, and are detected when human or animal disease starts to occur. Understanding the key properties of an EID is crucial to gauge the (human and veterinary) public health response and to come up with proportionate, effective and acceptable control measures. This can be quite challenging during early stages of an EID when little is known, media may influence the public debate, and authorities are pressed for decision making. Optimally, the NCOH will have an integrated research agenda to address key questions arising during an EID event that can support development of tools to detect and monitor the disease and provide input for modelling of disease spread and interventions.

The goal of our research in this Solution Set for NCOH-EID is (1) to identify and understand the key factors that render pathogens with human pandemic potential prone to cross the species barriers, adapt to the human host and further to gain human-to-human transmissibility, and (2) to translate our increased understanding of key factors in the chain of emergence to risk assessment, and options for prevention and intervention of human pandemics emerging from such pathogens.

### 4.8 Rapid clinical research to inform clinical management and public health measures upon EID emergence.

In the event of a (re-)emerging epidemic, it is essential to gain rapid insights into the risks and modes of transmission, the clinical spectrum, as well as the risk factors and pathogenesis of severe disease development, in order to optimize clinical management and public health strategies. However, clinical research efforts are usually too late to provide such insights in a timely manner, hence capacity for rapid clinical research responses during epidemics needs improvement. The establishment of such capacity across Europe is the focus of the EU-funded PREPARE project (www.prepare-europe.eu) in which three NCOH contributing partners participate prominently. PREPARE activities and infrastructure will be embedded in NCOH activities to strengthen EID clinical research preparedness in the Netherlands. Current research efforts in the developing clinical networks within PREPARE include observational studies to gain insights into the epidemiology and pathogenesis of several infectious disease syndromes of epidemic relevance (ARI, arboviral infections, CNS infections) as well as intervention studies in influenza and community acquired pneumonia in primary- and intensive care, respectively.

## 5. Research Project Portfolio of NCOH-SHF

### 5.1 Introduction to the NCOH-SHF Strategic Research Agenda

The goal of the NCOH-SHF is to improve animal health and reduce or eliminate human health risks arising from livestock and food production through use-inspired, fundamental, translational, and applied research, contributing to more robust animals, early signalling of health-disease status of the animal (animal signals of disturbance of health) with new biomarkers and smart and healthy farming practices. Core to the research agenda of the NCOH-SHF are the main causes of (perceived) human health risks and the accompanying debate on the license to produce sustainable and confronting the food production and processing sector. The NCOH-SHF will focus on the livestock sector as a primary source of the increasing demand for animal protein. The NCOH-SHF will address its overall goal through several, highly-interlinked Solution Sets (see Figure 8).

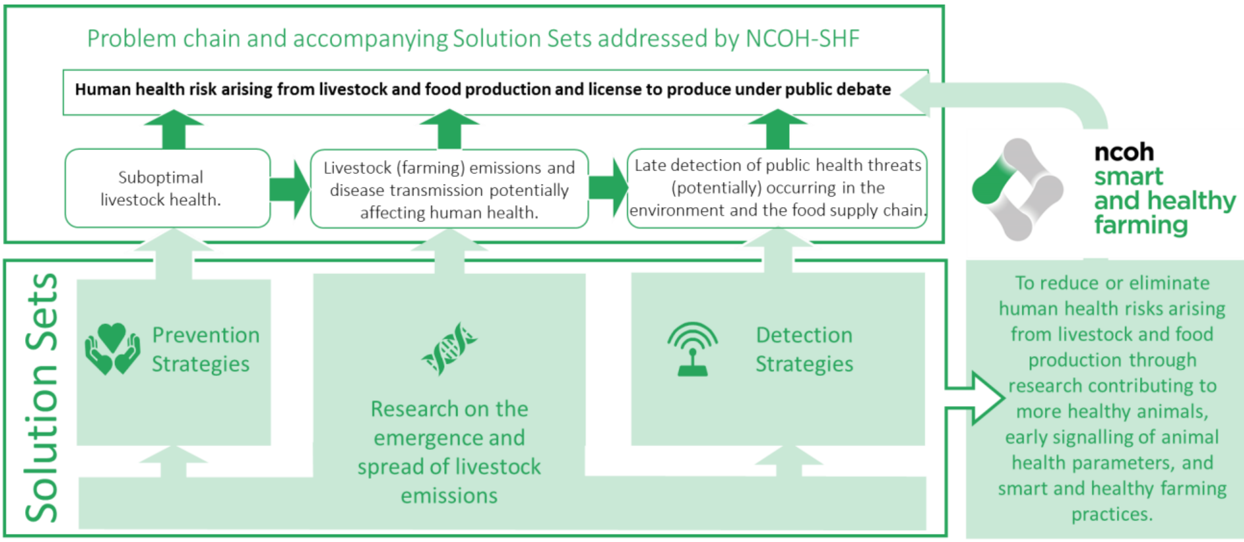


**Figure 8. Solution Sets of NCOH-SHF.**

1. Healthy Animals: Under the Solution Set *Prevention Strategies*, the NCOH-SHF will include research aimed at improving animal health, focusing on respiratory and intestinal health. Healthy animals are at the heart of the NCOH-SHF research efforts. By including research efforts directly aimed at improving the health and welfare of animals the NCOH-SHF attempts to hit three birds with one stone. Healthy animals that are more resilient against disease, in combination with increased animal welfare, will (i) decrease the need for antibiotics, (ii) increase consumer confidence, and (iii) reduce the health risks from livestock emissions of infectious microorganisms, thereby reducing the impact on human health. In addition, it will lead to enhanced food safety through reduction of contamination of animal food products, thereby reducing exposure of consumers to pathogens and microorganisms resistant to antimicrobials.

2. Environmental Health Risk Reduction: the NCOH-SHF will focus of *Research on Drivers of Emergence and Spread* of livestock-related microorganisms through the food chain and through emission in the environment and resulting food consumption that create potential risks for human health. When relations between these food- and emission-related exposures and human health have been established objectively, preventive strategies can be developed that are based on the principles of healthy and robust animals and smart farming or strategies beyond these domains; by modification of housing and production systems and herd management to reduce emissions and improve animal health.

3. Detection strategies: detection strategies for early signalling of health-disease status of the animal (animal signals of disturbance of health) with new biomarkers and smart and healthy farming practices. Smart Farming is the term used for management of livestock making use of automated real-time monitoring and controlling of animal production, health, welfare, and environmental impact. Smart Farming solutions should include detection/signalling systems for animal signals of disturbance of health to predict whether livestock are healthy or infected or release more endotoxins and other emission factors that can cause human health problems. Food safety not only applies to food of animal origin. Human health risks related to food products will increase when climate change influences the enumeration of moulds and the production of mycotoxins. These toxins can through animal feed influence animal health and in the end influence human health. Effective control systems have to be developed to control these threats to human and animal health.

## 5.2 NCOH-SHF: Prevention Strategies (PS)

During the last decades, prevention of (intestinal and respiratory) animal diseases by other means than vaccination and improved diagnostics received very little attention. Nevertheless a variety of options exist to improve the intrinsic properties of animals for reducing the susceptibility (= improved resilience or adaptation capacity or robustness) of animals for (zoonotic) disease thereby avoiding conditions that require the use of antibiotics. These intrinsic properties may be modulated by management, programming, nutrition, and genetic selection. Although this does not sound as an innovative approach, research of the last decades did not take into account the important role of the interaction between environment, microbiota, immune system, and host. Enhancing animals' ability to resist and overcome diseases will help them to stay healthy and well adapted to their living conditions, i.e. increase their robustness and resilience. To accelerate progress in this field a particularly important goal is to develop improved tools to speed up the identification and quantification immune competence / adaptability parameters and understand their meaning in the population. Progress in this area is crucial for the successful development of management, housing, nutritional and genetic approaches to improve immune competence / adaptability and herd immunity, in order to increase health and welfare and better prevent diseases. Furthermore it is required to understand the key pathophysiological and epidemiological factors that influence immune competence and adaptability during all periods of the animal's life cycle, thereby focussing on critical transition periods. Application of immune modulating factors at the population level must also be taken into account. Thus, epidemiological studies and modelling, to understand the effect of interventions at the population level is pivotal.

## 5.3 NCOH-SHF: Detection Strategies (DS)

Smart Farming is the term used for management of livestock making use of automated real-time monitoring and controlling of animal production, health, welfare, and environmental impact. Livestock production in the Netherlands takes place in a dense populated country, which creates ample opportunities for pathogen exchange between humans and animals. Detection/signalling systems are needed that can signal the health status of an animal thereby predicting whether livestock will be or is in an early state of infected here we will use new smart farming technologies and big data analyses. Food products from animals are still causing health risks for humans in particular due to exposure to commensal or pathogenic bacteria (e.g. Campylobacter, Salmonella), parasites (Toxoplasma), viruses (e.g. hepatitis E) and antibiotic resistant bacteria that are a source of resistance genes. Controlling these hazards with detection strategies is a food chain responsibility, starting at the farm level and ending at the consumer level. Within this Solution Set, the NCOH-SHF will focus on the development of new cheap rapid high throughput technology with newly developed biomarkers that are correlated with health status and exposure reduction and prevention (emission reduction, new housing systems) measures and food safety detection systems.

## 5.4 NCOH-SHF: Underpinning Research (UR)

The NCOH-SHF research project portfolio in this Solution Set focuses on environmental health risk reduction through investigating livestock-related microorganisms through the food chain and through emission in the environment and resulting food consumption that create potential risks for human health. When relations between these food- and emission-related exposures and human health have been established objectively, preventive strategies can be developed that are based again on the principles of healthy and robust animals and smart farming or strategies beyond these domains.

# 5. Research Project Portfolio of NCOH-HWE

## 6.1 Introduction to the NCOH-HWE Strategic Research Agenda

The goal of NCOH-HWE is to decrease the detrimental effects of wildlife-related disease on human health, livestock production systems and ecosystems through understanding, anticipation and (potential) prevention of environmental factors driving spread of wildlife diseases using an integrated, multidisciplinary approach. The NCOH-HWE will address its overall goal through the following Solution Sets (see Figure 9).

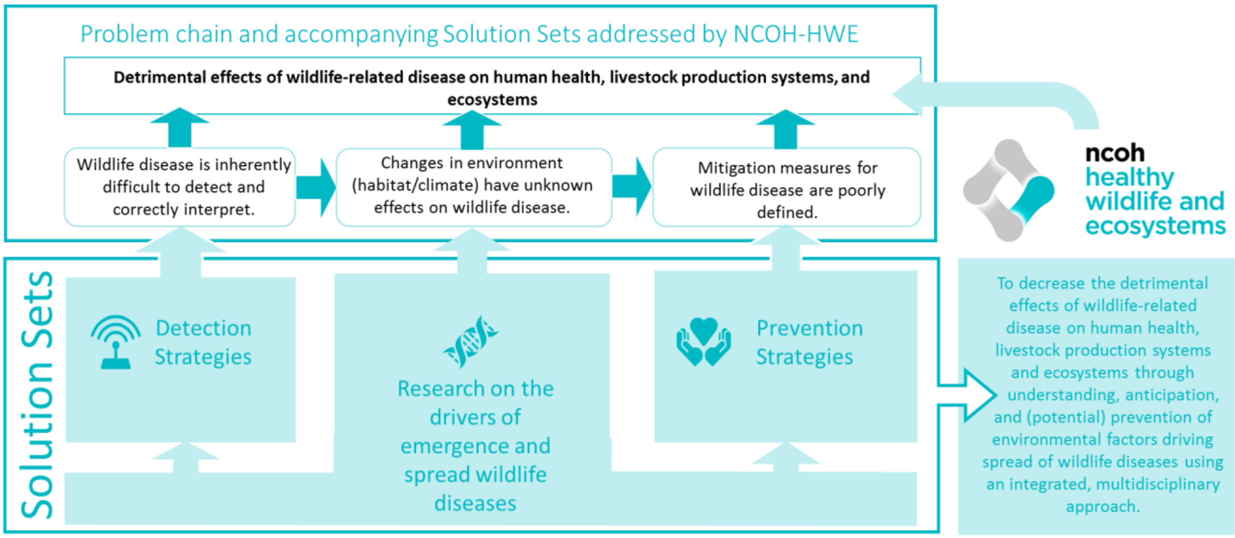


**Figure 9. Solution Sets of NCOH-HWE.**

1. Detection capacity: Adequate and timely detection of wildlife diseases, and sufficient detail in pathogen characterisation, is the starting point of NCOH-HWE research. Wildlife is inherently difficult to sample for appropriate testing, often elusive to general observation, and poorly investigated to date. Therefore improved detection strategies supported by new or improved diagnostic tools and methods are needed to maximise benefits and decrease costs are needed. . The NCOH-HWE will include research on one Solution Set: *Detection Strategies* in support of proper interpretation of wildlife disease occurrence and spread.

2. Analysis of drivers: The NCOH-HWE will include research on the Solution Set *Drivers of emergence and spread*. A better understanding of the drivers that influence wildlife host density, host movement, contact networks, community competence, and host-parasite interaction (e.g., under influence of vector ecology) is needed to better understand the changes in the spatio-temporal distribution of diseases. Changes in landscape configuration (e.g., habitat quality, fragmentation), ecosystem structure (e.g., species interactions), movement of hosts, parasites and vectors, and anthropogenic impacts (e.g., encroachment), under influence of changing climatic conditions, are major drivers of disease emergence.

3. Evidence-based management: Measures for wildlife disease management often focus not on the species itself but on management of their environment (e.g., water flow, pet trade, etc.), and contrary to domestic animals, wildlife population regulation measures have effect at time of peace rather than during outbreaks. Analysing the socio-economic consequences and gaining support from stakeholders and society for such measures is a challenge, and requires evidence-based understanding to argue and justify implementation. The NCOH-HWE will include research to document and provide evidence for appropriate *Prevention strategies* and to increase public support for associated Policy recommendations.

To materialize NCOH-HWE's ambition, the prime focus in the research priority areas in the beginning will be a set of specific diseases associated with typical landscape. Because of the interdependency of the solution sets, the Principal Investigators involved in research on a given landscape-disease tandem in the four Solution Sets will select a Coordinating Principal Investigator to ensure result.

Understanding the impact of the different players and factors in these complex diseases is a difficult task. The NCOH-HWE partners have a long history in investigating wildlife disease within monitoring programs and have built a tight collaboration network, involving various researchers from different fields. The partners are strong in modelling, analysing and quantifying the impacts of different variables at different spatial scales of organization, so that scenarios can be identified and tested with regard to the eradication or the control of a disease. Wildlife-related disease transmission is complex, influenced by a wide range of spatial and non-spatial factors operating at a variety of scales, studied by a variety of different disciplines. A systems approach is now widely adopted for studying and testing of scenarios for managing infectious diseases in animals and people. Such a system approach can integrate the various factors influencing disease transmission and prevalence in a complex wildlife-vector-human disease system that is characterized by important interactions between factors.

*Research done in five complementary combinations of landscapes/infectious diseases*

By focusing on a variety of Dutch landscapes that are home to different parasites, vectors, and hosts, the NCOH-HWE can offer new insights. By focusing on the three dominant Dutch landscapes (urban, agricultural, and forested landscapes) we will be better prepared to control and mitigate future emerging diseases in the Netherlands at the wildlife, livestock, people interface. The landscape/disease tandems under investigation are:

- **Urban areas/toxoplasmosis.** The ambition is to quantify the different infection pathways and to identify key points in the urban transmission cycle where preventive measures can be taken, with special attention to rodents and rodenticides and the feral cat population that increases the chances of people to become infected with toxoplasma.
- **Agricultural areas & water bodies/tularemia.** The sudden emergence of tularemia in the Netherlands and other European countries offers a unique possibility to learn more about the spread of a disease involving multiple players such as multiple wildlife species and vectors under influence of changing environmental conditions.
- **Forest/wild boar diseases, co-infections.** understand the influence of landscape factors and control measures on the spread of wild-boar-associated diseases, through changes in contact network, host densities and dispersal, and to investigate how parasite co-

infection influence host susceptibility, competence for certain diseases and the effect these parasites have on host condition and contact networks.

- **Various landscapes/Lyme.** Understand the impact of the various risk factors involved in targeting areas with low deer densities and high and low rabbit densities, combined with an experimental approach in which we can control the densities of hosts to minimize the effect of confounding variables, to better understand how host community composition influences Lyme prevalence.
- **Wetlands/Influenza A viruses in wild birds**. Improving the understanding of immunity in IAV infection of wild birds to allow the development of an improved diagnostic test for evidence of past infection. Such a test would have wide application, because samples for IAV surveillance in wild water birds are collected worldwide.

## 6.2 NCOH-HWE: Detection Strategies (DS)

It is inherently difficult to detect and assess disease in wildlife due to the problem of representative sampling, absence of validated tests, general lack of knowledge of wildlife disease including specificity of pathogens and host immunity, and absence of reliable population data needed for appropriate sampling.

## 6.3 NCOH-HWE: Underpinning Research (UR)

Wildlife disease emergence and spread is driven by host and vector densities, dispersal and species interactions in their different environments, under influence of ecological conditions. Research starts with collecting prevalence data in hosts and vectors and documenting host contact patterns, specific situations of reservoir hosts, presence of pathogens in the environment and the effects of management practices.

## 6.4 NCOH-HWE: Prevention Strategies (PS)

When measures for wildlife disease management focus on the host and parasite itself, this often requires that its environment needs to be taken into account. Management of their environment (e.g., water flow or vegetation management, landscape connectivity etc.), is often more effective but requires a thorough cost-benefit evaluation. Strategies will be developed using the previously collected information on disease prevalence, drivers of emergence and spread, contact patterns and vector dynamics and competences. The tracks within this portfolio will be developed depending on the outcome of the two previous portfolios.

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