NRS Roadmap Respiratory Infections report

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1. Inventory of Dutch research efforts in this field over the past 5 years (2008-2013) by ISI web of knowledge

Search terms:
For an overview of research into respiratory infections the Web of Science was searched, in which we analysed data from the last 5 years only. Respiratory infection/Netherlands resulted in 603 original manuscripts. We addressed the categories “immunology, infectious disease, virology, microbiology and respiratory system”, also refined searches for “immune, bacteria, virus, fungi” and assessed the most frequent cited publications to get a clue on impact. Subsequently we searched for specific diseases (CF, tuberculosis, pneumonia, asthma and COPD, when needed refined for infection) and here too assessed the number of citations.

The sheer numbers of publications and citations indicate that research into respiratory infections is prominent in the Netherlands, although numbers are similar or slightly under those of several other European countries (UK, France, Germany, Spain, Italy). A large number of publications have an international basis. There are several groups (selection of which mentioned below) that have their mainstream research into the searched categories, but there are numerous groups that contribute to the searched area from different areas such as basic mechanisms.

Top cited articles
Most infection studies are in the fields of pneumonia and tuberculosis. Pneumonia: (v.d Poll, AMC, mechanistic/translational; Goossens, UMCU, primary care/trials). Tuberculosis (van Soolingen, RIVM, bacteriology/epidemiology; Ottenhoff, LUMC, host defense and immunogenetics; Borgdorff, AMC, epidemiology/diagnostics). Whereas asthma and infections results in 115 publications (de Jongste, EUR, clinical/translational; Brunekreef, UMCU, epidemiology; Kimpen, UMCU, clinical/mechanistic), both CF and infections (45; v,d Ent, UMCU, clinical) and COPD (40; Boersma, clinical, MCA) lack behind.

Within the context of respiratory infections, but from the pathogen's point of view virology is strongly represented. Osterhaus (EUR; virology, epidemiology) and v.d Hoek (AMC, virology). Bacteriology (Bonten, UMCU, bacteriology) and fungi are less often represented.

Summary

Overall research input dedicated to respiratory infections is in line with that in other European countries. Clinical and epidemiological studies are mainstream, followed by characterization of the pathogens. The cross talk between various disciplines that is seen for tuberculosis (clinic, characterization of pathogen, basic mechanisms) is missing or only just beginning to emerge for other respiratory diseases. Relevant basic mechanisms are being studied but often from the perspective of innate/adaptive immune mechanisms, and thus less embedded in clinical studies.

2. Visibility Dutch research judged by international experts (see also Appendix)

Areas with good visibility	**Less visible**
Epidemiology and control	Lack of pulmonology involvement
Host pathogen interaction	
Omics technology	
Clinical RCT's Patient registry / data management	

3. Research needs

Facts and figures

Community Acquired Pneumonia (CAP)

- The incidence of community-acquired pneumonia (CAP) is 10.3 per 1,000 males and 10.8 per 1,000 females per year based on registration by GP's (2007).
- The incidence increases with age, resulting in incidence of 17.8/1.000 at 65-69 years and 63.0/1,000 at 85 years and older.
- In 2011 5,000 patients died as direct complication of CAP, with highest rate in pneumococcal pneumonia and legionella pneumonia.
- Approximately 90% of all deaths are patients of ≥ 65 years of age.
- Compared to other European countries CAP mortality in the Netherlands ranges in a middle position 2009: 20.2/100,000 people)
- Antibiotic resistance in the Netherlands is far lower compared to South European countries.
- It has been expected that lower respiratory tract infections will increase by 13% between 2005 and 2025.

Euro costs[2]

- The total costs of influenza and CAP was 630 million euro's in 2007, which is 0.8% of the total health costs in the Netherlands. 62% of all costs are related to diagnostic procedures and treatment (acute and chronic) in patients aged over 70.
- More than 50 % of CAP related costs are costs related to referral and admission to hospitals.

Unmet needs (extracted from: LAN rapport 2010[3])

Tuberculosis

- In 2010 44% of all TB patients in the Netherlands were diagnosed as pulmonary tuberculosis; 12% had tuberculosis of different organs including the lung.[1]
- In 2009 1,158 new TB cases were registered (incidence 7 per 100,000 inhabitants).
- 45% of these new patients are born outside the Netherlands.
- Sixty-six percent of all Dutch TB patients have been imported.
- The highest incidence (7/100,000) of non-imported cases is found in patients aged of 65 years and older.
- In 2010 54 patients died because of TB of whom 44% had pulmonary tuberculosis.
- The highest incidence of tuberculosis is found in former Soviet countries.

- Globally, in 2010 multidrug resistance (MDR) was diagnosed in 3.6% of all new patients and 20% of already treated patients. The highest levels of MDR-TB are in eastern Europe and in Central Asia, where in several countries, more than 20% of new cases and more than 50% of previously treated cases have MDR-TB. . Especially, extended drug resistance (XDR) is of major concern.
- In 2011, 15 of the 1012 patients in the Netherlands were diagnosed as MDR-TB. None had XDR-TB.

Euro costs[2]
The costs of TB in the Netherlands in 2007 was 54.5 million Euros and is 5.1% of all costs of infectious diseases.
80% of all costs consisted of public health and prevention. Hospital related costs are only 16% of all costs.
Tuberculosis contributed in 2007 to approximately 610 DALY's ('Disability-Adjusted Life-Years').[2]

References
[1]Feiten en cijfers chronische Longziekten (LAN 2013).
[2]Gommer AM (RIVM), Poos MJJC (RIVM), Hoeymans N (RIVM). Verloren levensjaren, ziekte en ziektelast voor 56 geselecteerde aandoeningen. In: Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid. Bilthoven: RIVM maart 2010 (www.nationaalkompas.nl/gezondheid-en-ziekte/sterfte-levensverwachting-en-daly-s/ziektelast-in-daly-s/ verloren-levensjaren-ziekte-en-ziektelast-voor-56-geselecteerde-aandoeningen)
[3]Feiten en cijfers chronische Longziekten (LAN 2010)

Other respiratory related infectious diseases
Infectious respiratory diseases are part of different other diseases, such as acute exacerbation of COPD (viral, bacterial), hospital related infections (nosocomial pneumonia, ventilator associated pneumonia) and simple bronchitis. These infections are not highlighted in LAN 2013, but especially hospital related respiratory infections are associated with high mortality and also high costs.

4. Summary SWOT analysis

Strengths 1. Biological mechanisms 2. Diagnosis and monitoring 3. Therapy medical	*Weaknesses* 1. Implementation and care 2. Biobanking 3. Development and ageing
Opportunities 1. Data management 2. Biobanking 3. Prevention	*Threats* 1. Therapy medical 2. Data management 3. Development and ageing

Relevance of research judged by international experts (order of importance)
See Table *Relevance of research judged by international experts* in appendix

	Mean
Phenotyping and Severity	3.50
Biological mechanisms	3.50
Environment and lifestyle	2.50
Development and ageing	3.00
Prevention	4.25
Diagnosis monitoring	4.25
Therapy medical	4.25
Therapy non-medical	2.75
Biobanking	2.50
Data management clinical studies	3.25
Implementation and care	4.00

5. Description of the interface of Respiratory Infections with other Roadmap areas

Looking at our research inventory there is a research overlap with the following groups:
Asthma, COPD, CF, ICU, Lung transplantation and Paediatric lung diseases.
In particular the following themes of overlap were identified:

- Asthma, COPD, lung transplantation, CF and Paediatric lung diseases: viral infections
- COPD, CF, ICU: bacterial infections
- COPD, CF: non-TB infections

- Paediatric lung diseases: TB-infections, ICU, Lung transplantation, COPD, paediatric lung diseases: Parasitic infections

6. Priorities for Dutch research in the area for 2014-2019

- Intensively linking fundamental research with clinical research (also beyond diseases).
- Usage of phenotyping and biobanking data for studies (e.g. CAPNETZ group in Germany).
- More attention to studies in the field of prevention and ageing (e.g. vaccination).
- Attention to new threatening pathogens (viruses, TB: mechanisms, diagnosis, prevention, etc).
- Better cooperation between institutions including government and funding bodies.

7. What is needed to let the research priorities listed be successful?

- Independent institution that facilitates the input and use of data management phenotyping) and biobanking (e.g. clinical and epidemiological studies)
- More intensive cooperation between fundamental researchers and clinical researchers; create platforms for discussion.
- More intensive cooperation between university hospitals and general hospitals (CAPNETZ Germany)
- Structural funding for research in respiratory infections
- Better cooperation between institutions including government (i.e. implementation of national clinical surveillance (CAP, VAP, TB, …) and linkage to pathogen surveillance)

8. What do patients want?

We did some research. No clear information could be provided by the Longfonds. Speculating, one of topics that may have special interest in the elderly is influenza and pneumococcal vaccination.

Table 1 . Top 10 most cited basic research initiated by a Dutch group*:

Theme	Article	Citations	
		Total	Mean/yr
resp. infections; virolog	Herfst, S, Chutinimitkul, S, Jianqiang, Y.E, et al. Introduction of virulence markers in pb2 of pandemic swine-origin influenza virus does not result in enhanced virulence or transmission. Journal of Virology. 2010; 84: 3752.	54	18.0
resp. infections; immunology	Belderbos, M.E, Van Bleek, G.M, levy,O, et al. Skewed pattern of toll-like receptor 4-mediated cytokine production in human neonatal blood: low lps-induced il-12p70 and high il-10 persist throughout the first month of life. Clinical Immunology. 2009; 133: 228.	50	12.5
resp. infections; virology	Dijkman,R, Koekkoek, S.M, Molenkamp, R, et al. Human bocavirus can be cultured in differentiated human airway epithelial cells. Journal of Virology. 2009; 83: 7739-7748.	48	12.0
resp. infections; virology	Lukens, M.V, Kruijsen, D, Coenjaerts, F.E.J, et al. Respiratory syncytial virus-induced activation and migration of respiratory dendritic cells and subsequent antigen presentation in the lung-draining lymph node. Journal of Virology. 2009; 83: 7235-7243.	43	10.8
resp. infections; immunolog	Van Zoelen, M.A.D,Schouten, M, De Vos, A.f, et al. The receptor for advanced glycation end products impairs host defense in pneumococcal pneumonia Journal of Immunology. 2009; 182: 4349-4356.	37	9.3
resp. infections; immunology	Kreijtz, J.H.C.M, Suezer, Y, De Mutsert, G, et al. Recombinant modified vaccinia virus ankara expressing the hemagglutinin gene confers protection against homologous and heterologous h5n1 influenza virus infections in macaques. Journal of Infectious Diseases. 2009; 199: 405-413.	37	9.3
resp. infections; infectious diseases	Kreijtz, J.H.C.M, Suezer, Y,De Mutsert, G, et al. Recombinant modified vaccinia virus ankara expressing the hemagglutinin gene confers protection against homologous and	37	9.3

	heterologous h5n1 influenza virus infections in macaques. Journal of Infectious Diseases. 2009;199: 405-413		
resp. infections; immunology	Kreijtz, J.H.C.M., Bodewest, R, Van Den Brand, J.M.A., et al. Infection of mice with a human influenza a/h3n2 virus induces protective immunity against lethal infection with influenza a/h5n1 virus. Vaccine. 2009; 27:4983	34	8.5
resp. infections; immunology	Van den Brand, J.M.A, Stittelaar, Koert j, Van Amerongen, G, et al. Severity of pneumonia due to new h1n1 influenza virus in ferrets is intermediate between that due to seasonal h1n1 virus and highly pathogenic avian influenza h5n1 virus. Journal of Infectious Diseases. 2010; 201: 993-999	6	2.0

* Respiratory infections comprise viruses, bacteria, fungi, are found in virtually every respiratory disease and are studied from an epidemiological perspective to the molecular level. The team found it extremely difficult to cover this heterogeneous field fully. Publications from last 5 years were taken. Therefore, a number of publications, especially in basic research but also link to other respiratory illnesses may be missed.

Table 2. Top 10 most cited clinical research initiated by a Dutch group:

Theme	Article	Citations	
		Total	Mean/yr
Resp. infections; immunology; infectious diseases	Meijer, A, Lackenby, A, Hungnes, O, et al. Oseltamivir-resistant influenza virus a (h1n1), europe, 2007-08 season. Emerging Infectious Diseases. 2009; 15: 552-560.	183	61.0
Resp. infections; microbiology	Van Boheemen, S, De Graaf, M, Lauber,C, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. Mbio. 2012; 3	47	47.0
Resp. infections; Resp. system	Snijders, D, Daniels, J.M.A, De Graaff,C.S, et al. Efficacy of corticosteroids in community-acquired pneumonia a randomized double-blinded clinical trial. American Journal of Respiratory and Critical Care Medicine. 2010; 181: 975-982.	62	20.7
Resp. infections; Resp. system	Oostdijk, E.A.N, De Smet, A.G.A, Blok, H.E.M, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. American Journal of Respiratory and Critical Care Medicine. 2010; 181: 452-457	61	20.3
Resp. infections; infectious diseases	De Smet, A.G.A, Kluytmans, J.A.J.W, Blok, H.E.M, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infectious Diseases. 2011; 11: 372-380.	36	18.0
Resp. infections; immunology; infectious diseases	Gooskens, J, Jonges, M, Claas, E.C.J, et al. Prolonged influenza virus infection during lymphocytopenia and frequent detection of drug-resistant viruses. Journal of Infectious Diseases. 2009; 199 1435-1441.	51	17.0
Resp. infections;	Jansen, R.R, Wieringa, J, Koekkoek, S.M, et al. Frequent detection of respiratory viruses	34	17.0

microbiology	without symptoms: toward defining clinically relevant cutoff values. Journal of Clinical Microbiology. 2011; 49: 2631-2636.		
Resp. infections; Resp. system	Van Ingen, J,Bendien, S.A, De Lange, W.C.M, et al. Clinical relevance of non-tuberculous mycobacteria isolated in the nijmegen-arnhem region, the netherlands. Thorax. 2009; 64: 502-506	46	11.5

Table 3. Top 10 most cited collaborative international basic research (excl. reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/yr
Tuberculosis	Caccamo, Nadia; Guggino, Giuliana; Joosten, Simone A.; et al. Multifunctional CD4(+) T cells correlate with active Mycobacterium tuberculosis infection. European Journal of Immunology. 2010; 40: 2211-2220	71	23.7
resp. infections; virology	Lemon, K.; De Vries, R.D.; Mesman, A.W.; et al. Early target cells of measles virus after aerosol infection of non-human primates. Plos Pathogens. 2011	40	20.0
resp. infections; immunology	Walsh, K.P, Brady, M.T, Finlay, C.M, et al. Infection with a helminth parasite attenuates autoimmunity through tgf-beta-mediated suppression of th17 and th1 responses. Journal of Immunology. 2009; 183: 1577-1586.	71	17.8
resp. infections; immunology	Mcgill,J, Van Rooijen, N, Legge, K.L. Il-15 trans-presentation by pulmonary dendritic cells promotes effector cd8 t cell survival during influenza virus infection. Journal of Experimental Medicine. 2010; 207 521-534.	43	14.3
resp. infections; infectious diseases	Reichert, T, Chowell,G, Nishiura,H, et al. Does glycosylation as a modifier of original antigenic sin explain the case age distribution and unusual toxicity in pandemic novel h1n1 influenza? BMC Infectious Diseases. 2010; 10	42	14.0
resp. infections; virology	Tate, M.D, Pickett, D.L, Van Rooijen, N, et al. Critical role of airway macrophages in modulating disease severity during influenza virus infection of mice. Journal of Virology. 2010; 84: 7569	40	13.3

resp. infections; immunology	Vergunst, A.C, Meijer, A.H, Renshaw, S.A. et al. Burkholderia cenocepacia creates an intramacrophage replication niche in zebrafish embryos, followed by bacterial dissemination and establishment of systemic infection. Infection and Immunity. 2010; 78:1495-1508.	27	9.0
resp. infections; immunology	Martelli, P, Gozio,S, Ferrari, L, et al. Efficacy of a modified live porcine reproductive and respiratory syndrome virus (prrsv) vaccine in pigs naturally exposed to a heterologous european (italian cluster) field strain: clinical protection and cell-mediated immunity. Vaccine. 2009; 27: 3788-3799.	34	8.5
resp. infections; virology	Rockx, B, Baas, T, Zornetzer, G.A, et al. Early upregulation of acute respiratory distress syndrome-associated cytokines promotes lethal disease in an aged-mouse model of severe acute respiratory syndrome coronavirus infection. Journal of Virology. 2009; 83: 7062-7074	31	7.8

Table 4. Top 10 Most cited collaborative international clinical research (excl, reviews, guidelines):

Theme	Article	Citations	
		Total	Mean/yr
resp. infections; infectious diseases	Dawood, F.S, Iuliano, A.D, Reed, C, et al. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza a h1n1 virus circulation: a modelling study. Lancet Infectious Diseases. 2012; 12: 687-695	46	46.0
resp. infections; infectious diseases	Bermingham, A, Chand, M.A, Brown, C.S, et al. Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the united kingdom from the middle east. Eurosurveillance. 2012; 17 : 6-10	37	37.0
resp. infections; resp. system	Thomsen, S.F, Van der Sluis, S, Stensballe, L.G, et al. Exploring the association between severe respiratory syncytial virus infection and asthma a registry-based twin study. American Journal of Respiratory and Critical Care Medicine. 2009; 179:1091-1097	50	12.5
resp. infections; microbiology	Gaunt, E.R, Hardie, A, Claas, E.C.J. et al. Epidemiology and clinical presentations of the four human coronaviruses 229e, hku1, nl63, and oc43 detected over 3 years using a novel multiplex real-time pcr method. Journal of Clinical Microbiology. 2010; 48: 2940-2947	28	9.3
resp. infections; microbiology	Gadsby, N.J, Hardie, A, Claas, E.C.J, et al. Comparison of the luminex respiratory virus panel fast assay with in-house real-time pcr for respiratory viral infection diagnosis. Journal of Clinical Microbiology. 2010; 48: 2213-2216	27	9.0
resp. infections; resp. system	Pinnock, H, Thomas, M, Tsiligianni, I, et al. tThe international primary care respiratory group (ipcrg) research needs statement 2010. Primary Care Respiratory Journal. 2010; 19	23	7.7

resp. infections; infectious diseases	Kajon, A.E, Lu, X, Erdman, D.D, et al. Molecular epidemiology and brief history of emerging adenovirus 14-associated respiratory disease in the united states. Journal of Infectious Diseases. 2010; 202: 93-103	21	7.0
resp. infections; infectious diseases	Ison, M.G, De Jong, M.D, Gilligan, K.J. et al. End points for testing influenza antiviral treatments for patients at high risk of severe and life-threatening disease. Journal of Infectious Diseases. 2010; 201 1654	19	6.3

Table 5: Top 10 best cited review and guideline papers with Dutch collaborators:

Theme	Article	Citations	
		Total	Mean/yr
guideline	Woodhead, M, Blasi, F, Ewig, S, et al. Guidelines for the management of adult lower respiratory tract infections - Full version Group European Resp Soc; European Soc Clinical Microbiology. Clinical Microbiology and Infection. 2011; 17 E1-E59	47	23.5
review	Willems, R.J.L, Hanage, W.P, Bessen, D.E, et al. Population biology of Gram-positive pathogens: high-risk clones for dissemination of antibiotic resistance. Fems Microbiology Reviews. 2011; 35 872-900	45	22.5
review	Huttner, B, Goossens, H, Verheij, T, et al. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries Group CHAMP Consortium. Lancet Infectious Diseases. 2010; 10: 17-31	55	18.3
review	Kimman, T.G, Cornelissen, L.A, Moormann, R.J, et al. Challenges for porcine reproductive and respiratory syndrome virus (PRRSV) vaccinology. Vaccine. 2009; 27: 3704-3718	66	16.5
review	Kreijtz, J.H.C.M, Fouchier, R.A.M, Rimmelzwaan, G.F. Immune responses to influenza virus infection. Virus Research. 2011; 162: 19-30	33	16.5
review	Fang, Y,Snijder, E.J. The PRRSV replicase: Exploring the multifunctionality of an intriguing set of nonstructural proteins. Virus Research. 2010; 154: 61-76	48	16.0

review	Brusselle, G.G, Demoor, T, Bracke, K.R, et al. Lymphoid follicles in (very) severe COPD: beneficial or harmful? European Respiratory Journal. 2009; 34: 219-230	35	8.8
guideline	Pinnock, H, Thomas,M, Tsiligianni, I, et al. The international primary care respiratory group (ipcrg) research needs statement 2010. Primary Care Respiratory Journal. 2010; 19	23	7.7

APPENDIX

Opinions of international key opinion leaders

Questions were sent to international experts in the field about the visibility of Dutch Respiratory Infections research.

Question 1
Which research topics and groups in Respiratory Infections research are visible and have impact on pulmonary physicians and researchers outside the Netherland?

Expert

As pointed out above, there is an international impact of Dutch infectious disease research including a broad spectrum of topics.

Some topics that are on top in Europe and worldwide:

- Infection Epidemiology and Infection Control including huge clinical trials (Utrecht, Nijmegen, etc.)
  - Virus epidemiology, Emergent Infections (Rotterdam)
  - Host pathogen Interaction (Amsterdam, Groningen)
  - Omics Technology (Amsterdam, Groningen, in part Rotterdam)
  - Clinical RCTs in Pneumonia/AECOPD (Alkmaar, Amsterdam)

A specific strength in the Netherlands is a very good patient registry either in outpatients and in hospital admitted patients and a well-equipped data management and statistical analysis (Leiden, Julius Center, Utrecht).

Expert 2

Expert 3

RCTs of interventions
Community-acquired pneumonia
Lower respiratory tract infection in general practice
Nosocomial pneumonia (particularly prevention)
Antibiotic use
Environmental mycobacteria
Viral infections

Utrecht (Verheij, Bonten)
Alkmaar (Boersma)
Nijmegen (van Ingen)
Rotterdam (Osterhaus)

Expert 4

- Tuberculosis (my bias), Frank Cobelens, KNCV, Martien Boree

- Influenza: Rotterdam group

Question 2

Which research topics in Respiratory Infections research are less visible to physicians and researchers outside the Netherland?

Expert 1

Infectious disease is represented nearly in all universities. The publication impact and the grant income, mainly from EU grants is impressive.

The only concern is that infectious disease research is mainly driven by infectious disease departments, by microbiologists and virologists. There are some infectious disease specialists in pulmonary medicine, but the influence of pneumology in the whole field is quite low.

Expert 2

Expert 3

Tuberculosis
Infections in immunocompromised

Expert 4

- CAP, HAP
- Antibiotic resistance

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of Respiratory **Infections**

0= no relevant research
5= excellent research international top level

	1	2	3	4	Mean
Phenotyping and Severity	4	3	4	3	3.50
Biological mechanisms	5	3	2	4	3.50
Environment and lifestyle	4	2	1	3	2.50
Development and ageing	4	3	2	3	3.00
Prevention	5	3	5	4	4.25
Diagnosis monitoring	4	3	5	5	4.25
Therapy medical	4	3	5	5	4.25
Therapy non-medical	3	2	4	2	2.75
Biobanking	2	3	2	3	2.50
Data management clinical studies	2	3	3	5	3.25
Implementation and care	5	3	4	4	4.00