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Respiratory tract infection: prevention, early detection and attenuation of immune response

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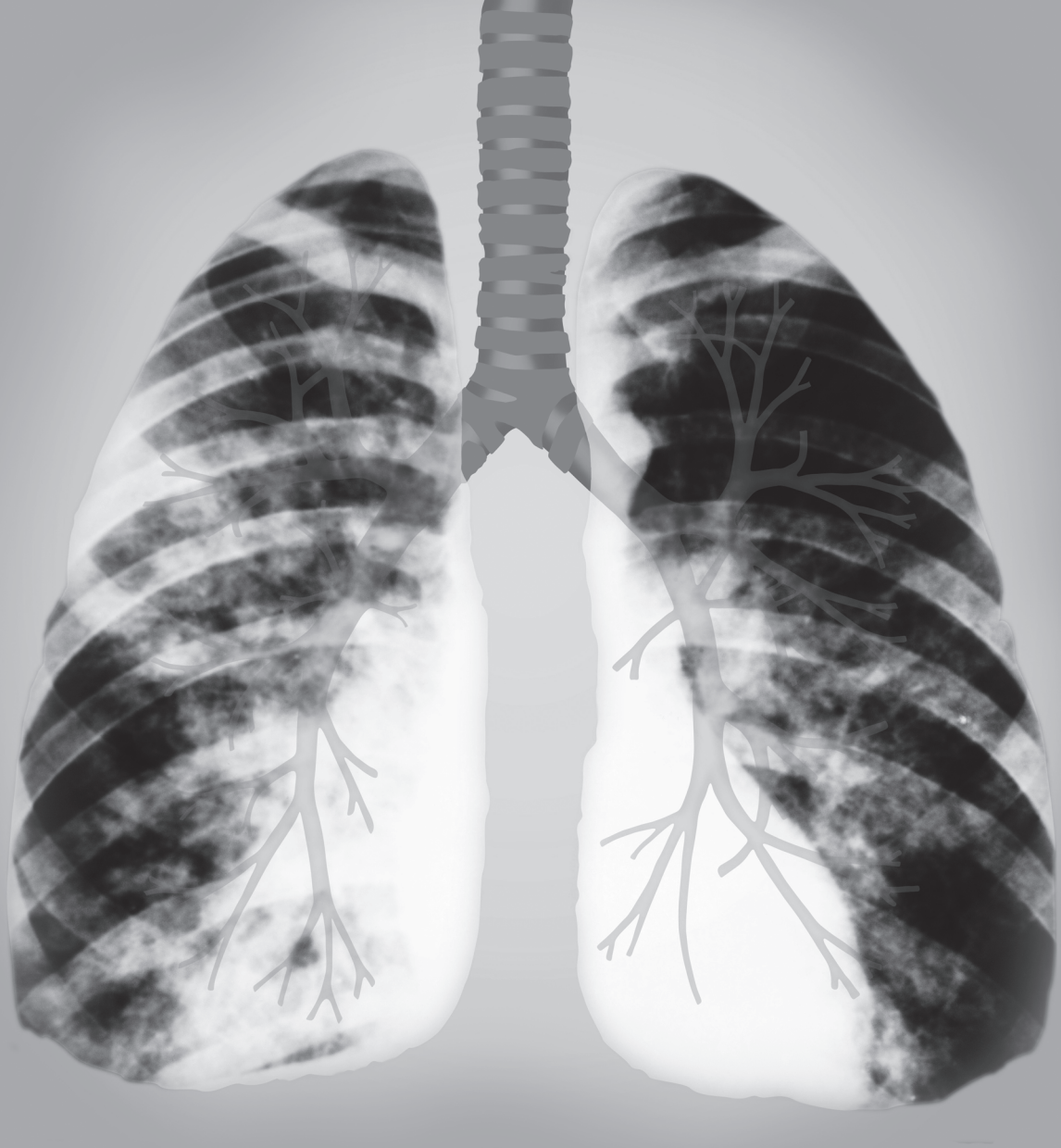

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Introduction and outline of this thesis

Respiratory tract infections

Respiratory tract infections are among the most common infections treated by health care practitioners. In this respect, a distinction is made between upper and lower respiratory tract infections. The tract is divided in an upper part above the vocal cords (including the nose and nasal passages, paranasal sinuses, the pharynx, and the portion of the larynx above the vocal cords) and a lower part, below the vocal cords (including the larynx below the vocal folds, trachea, bronchi, bronchioles, and alveoli). Lower respiratory tract infections (LRTI) occur frequently and can have severe consequences: they accounted for the largest part of infectious disease mortality in the United States (1) and globally (2), with only limited improvement in recent decades.

Two aspects characterise an infectious disease such as LRTI: the establishment of a microorganism on or within a host and (tissue) damage due to the replicating microorganism itself, its toxins, or the inflammatory response of the host to its presence. The combination of these aspects in the lower respiratory tract leads to bronchitis, bronchiolitis or pneumonia. Patients may present with acute disease (e.g., pneumococcal pneumonia) or chronic respiratory tract infection (e.g., tuberculosis). Acute lower respiratory tract infections are mostly defined by complaints lasting for less than three weeks. The host inflammatory response indirectly causes symptoms such as fever, and the local tissue damage and extension of the pulmonary infiltrate determine the intensity of coughing, production of sputum, shortness of breath, and sometimes, pleural pain.

Microbial aetiology

Viruses are the most common etiologic microorganisms causing acute lower respiratory tract infections. Various types of viruses may cause bronchitis, whereas some of these are also able to cause bronchiolitis or pneumonia. For example, human rhinovirus most often causes mild (upper respiratory tract infection or) bronchitis. Influenza virus and respiratory syncytial virus (RSV) may cause more severe bronchiolitis and pneumonia, but can also be found in the upper respiratory tract.

Viral infections may pave the way for bacterial ('super') infection, in particular in patients already colonized with bacteria because of an underlying disease such as COPD or bronchiectasis. Superinfection may result in pneumonia, and such bacterial infections may progress rapidly and result in severely ill patients. Common bacterial etiologic microorganisms are *Streptococcus pneumoniae*, *Haemophilus influenzae, Legionella pneumophila,* and *Mycoplasma pneumoniae*. Finally, fungi and parasites may cause pneumonia as well. However, these last infections occur predominantly in susceptible, immunocompromised hosts – due to underlying disease or immunosuppressive treatment – or are linked to exposure in a specific geographic area.

In the Netherlands, the average patient with a community-acquired acute lower respiratory tract infection most likely has a viral or bacterial cause of infection or a combined infection with both a virus and a bacterium (3-6). Yearly, such infections account for the admittance of about 50.000 individuals to hospitals in the Netherlands (www.zorgatlas.nl).

Host inflammatory response

Most body cells can detect the presence of microbes with pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) which recognize pathogen-associated molecular patterns (PAMPs) on the invading microorganisms. In respiratory epithelial cells, typically among the first cell types to become involved in a respiratory tract infection, the activation of these PRRs is essential in limiting the spread of pathogens and in triggering an immune response through the release of proinflammatory mediators (cytokines and chemokines). These mediators initiate host innate and adaptive immune responses that – in most cases – succeed in containing or killing a tissue-invading microorganism (7).

This host inflammatory response comes, however, at a cost, as in most cases at least some collateral damage to the tissue occurs that must be restored and may result in some form of permanent scar (e.g., bronchiectasis, pleural adhesions). An uncontrolled and/or exacerbated inflammatory response to the microorganism may be associated with severe acute lung injury (such as Acute Respiratory Distress Syndrome) and consequently, severe morbidity and mortality (8, 9). Ideally, the host response to infection should accomplish sterilisation of a local site of infection without causing collateral damage in the form of destruction of lung tissue and lung architecture (9). Therefore, a delicate balance between an adequate inflammatory response to eradicate the causative microorganism followed or accompanied by an anti-inflammatory response, causing cytokine neutralization and inhibition of macrophage recruitment to dampen the host immune response, is paramount.

Prevention of the most vulnerable by vaccination

Rather than treating and coping with consequences of respiratory tract infections, in many cases, it is possible to vaccinate against pathogens causing LRTI and thus prevent infection and its consequences altogether. For respiratory tract infections, vaccines against influenza, *Bordetella pertussis*, *Streptococcus pneumonia,* and *Haemophilus influenzae* are used in various target groups. Vaccination mimics natural infection in the sense that it primes the host immune system for an adequate enhanced response upon re-exposure to the pathogen, but this is accomplished without the morbidity and risks of natural infection. In addition to providing individual protection, vaccination – if the vaccination rate surpasses a certain level determined by the ease of transmission of the pathogen – may also protect individuals not yet immunized (or too young or unable to respond to vaccination) by

herd immunity. In addition, transplacental transfer of antibodies helps protect new-born infants whose mothers were vaccinated (against influenza and *Bordetella pertussis*) (10, 11). Finally, vaccination of close contacts of certain patients may prevent the introduction of a pathogen in the proximity of these patients, thus shielding off ("cocooning") the most vulnerable in a group or family. This strategy is relevant because vaccination of immunocompromised, frail, and elderly patients may be less effective in preventing infection as compared with their young and healthy close contacts that provide a 'cordon sanitaire'.

In this way, vaccination of household contacts and healthcare professionals against easily transmissible pathogens such as the influenza virus may help protect vulnerable patients by minimizing, or at least reducing, exposure to these pathogens. Already, influenza vaccination coverage is higher among persons living with or caring for vulnerable patients, as compared to the ones without the proximity of vulnerable patients (12). However, in healthcare settings, professionals – both physicians and nurses alike – are often not inclined to get the flu vaccination. In fact, influenza vaccine coverage among healthcare professionals taking care of the most vulnerable patients is very low. Among healthcare workers in Europe, the coverage was below 30%, and in Dutch hospitals in 2012, median vaccination coverage amounted to 13% (13, 14) while more recently the coverage in Dutch hospitals appears to equal European levels. Still, the low acceptance of vaccination such as the one against influenza goes against the principle of always delivering safe care and puts vulnerable patients at risk of acquiring influenza infection during hospital care (15, 16).

In the case of health care providers, influenza vaccination also touches upon other issues, such as absenteeism from work, need for fellow workers to fill in, and the continuation of care at a time it is needed most. During the yearly influenza season, especially in severe seasons, hospitals struggle to meet the demand for care. Due to influenza virus infection and the complications thereof, increased numbers of patients present to hospital for admission in acute care settings. Unfortunately, healthcare staff absenteeism is highest during the peak of the influenza season, and this reduces capacity in hospitals and other (health) care facilities. To meet the demand for, and deliver adequate care without potentially harming patients, an improvement of influenza vaccination coverage among health care workers is urgently needed.

Prevention by vaccination in patients with a stimulated immune system

Besides anti-infective properties, the immune system plays a critical role in fighting off cancer, for example, by detecting and controlling the proliferation of malignant cells (17, 18). T-cells are key players in the anti-tumor immune response, and these cells have, therefore, been an important target for immunotherapeutic interventions. Tumor cells

interfere with immune checkpoints on activated T cells to trigger inhibitory pathways that downregulate the intensity and the extent of the immune response, thus providing tumor cells with the chance to proliferate. In recent years, it was shown that the anti-tumor response of the immune system could be enhanced by blocking these immune checkpoints, thereby 'unlocking' the cell-mediated anti-tumor activity. Immunotherapy has become standard treatment for several malignancies across all tumor stages, for example, for lung cancer, melanoma, and head and neck cancer. Interestingly, the pro-inflammatory potential of checkpoint inhibitors leads to various (auto-)immune-related adverse events (e.g., colitis, encephalitis, pneumonitis).

Influenza vaccination can prevent not only respiratory tract infection but also cardiovascular (and all-cause) mortality in patients with heart failure (19) and the need for interruption of chemotherapy treatment in cancer patients (20). Therefore, patients under treatment for cancer may benefit from yearly influenza vaccination and are elected to get this vaccine by the Health Council of the Netherlands and the Dutch National Institute for Public Health and the Environment (21, 22).

In 2018, a Swiss research group described an increased incidence of checkpoint inhibitors-use related side effects after influenza vaccination in a small cohort (n=23) and they discussed the potential causality between these two interventions (23).

Uncertainty as to the consequences of the findings of the Swiss study led to reluctance of pulmonologists and oncologists to advise patients treated with checkpoint inhibitors to get their yearly influenza vaccination. A reduced influenza vaccination coverage in these patients may increase influenza infections among them and, with that, may cause more interruptions of cancer treatment and more admissions for influenza-like illness in these vulnerable patients (24), and by consequence, worse treatment outcomes.

From an immunological standpoint, one can argue that T cell enhancement during influenza vaccination should increase immunization and protection. That way, this immunotherapy with checkpoint inhibitors may be regarded as a vaccine adjuvant. Clearly, mechanistic studies in this field are urgently needed. Likewise, a potential causal relation between immune-related adverse events after influenza vaccination in patients treated with various immunotherapies for cancer needs to be examined.

Outbreak control by improved detection and monitoring

Once a contagious infectious disease occurs within a community, measures to monitor and contain the impact and dissemination of the disease must be put into effect. In the Netherlands, this is taken up by various parties. Locally, by public health care authorities

that survey and notify specific diseases, and nationally, by the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment that is responsible for organizing year-round surveillance and prepare-and-response to potential outbreak signals notified by the local authorities. In this way, the early detection of outbreaks is possible. After the large Legionella outbreak at the flower show in Bovenkarspel in 1999 (with 188 cases, 163 hospital admissions, and 21 deaths; case-fatality rate of 11%) (25), improvements in outbreak detection were implemented. Still, at the local and regional level, there are ample pitfalls of these systems that may delay outbreak detection:

- Microbiological diagnostics are time-consuming, especially in patients with uncommon presentations of common diseases.
- The list of notifiable diseases is limited.
- New, emerging infectious diseases may present as unknown syndrome, and this may delay outbreak detection.
- Patients of an outbreak may present at different health care institutions. The (extent of an) outbreak is not evident for an individual institution.

The Dutch Public Health Act obliges medical doctors to notify local public health authorities in case of an unusual number of patients with an infectious disease (26). In daily practice, this reason for notification is hardly ever used.

Most of these notifications are labor intensive and depend on the swift action taken by doctors or representatives of microbiological laboratories. With curative care and public health increasingly digitized in the last 20 years, the outbreak control methods should be modernised as well. For instance, signs and warnings of a (potential) local outbreak of infectious disease might be derived straight from the curative care record, and preferentially should appear “automatically” at the desk of local public health care authorities, without delay. Unfortunately, a tool like that is not available in the Netherlands but if developed, would improve early detection of infectious disease outbreaks and thereby, preclude spread at the earliest possible stage.

Some outbreaks tend to occur yearly at predictable seasons, as is the case with acute respiratory tract infections such as influenza and RSV. To manage and mitigate the potential impact of these outbreaks on curative care institutes, both early detection, and monitoring of the outbreaks are important. Until recently, surveillance of acute respiratory tract infections in the Netherlands consisted of monitoring the prevalence of influenza-like illness in primary care and through influenza-associated mortality surveillance (27, 28). Surveillance of Severe Acute Respiratory Infections (SARI), the infections for which hospitalization is necessary (29), was regarded as the missing link in the surveillance pyramid (30). SARI surveillance is deemed necessary to be able to execute preventive measures

timely, to assess the impact of these measures in the high risk (hospitalized) population, and to inform policymakers about the start, progress, and the extent of an outbreak in secondary care.

The World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) guided countries to set up SARI surveillance (31, 32). SARI surveillance is a relatively new surveillance method, and experience with these data is limited. To evaluate the potential added value of SARI surveillance, a comparison between primary care influenza-like illness surveillance and SARI surveillance should identify strengths and weaknesses, and determine the added value of the SARI surveillance on top of the current surveillance in primary care. It is, for example, currently unclear whether the incidence of influenza virus infection in general practice corresponds with the incidence in hospital admission for acute respiratory tract infection. Moreover, based on SARI surveillance hospitals may be urged to pursue additional hygienic measures for patients with influenza virus infection, perhaps segregate these patients, and empirically prescribe oseltamivir (a neuraminidase inhibitor) when there is a reasonable pre-test probability that a patient has an influenza virus infection. Thus, any discrepancy in the occurrence of the start and peak of influenza infections in general practice and the hospital influenza season could have major implications for the timing of these measures.

Detection of lower respiratory tract infection in primary care

In an individual patient with an acute respiratory tract infection, clinical signs and symptoms cannot distinguish between the various causative agents of the infection (33, 34). In primary care, microbiological diagnostics are not recommended because it is difficult to obtain an adequate sputum sample for culture, (pneumococcal) urinary antigen tests lack sensitivity, all diagnostic procedures take time, and most often, because even advanced, intense testing may fail to identify the causative agent. Also, and perhaps most significantly in this respect, the outcome of microbiological diagnostics will not affect patient treatment (which is based on clinical presentation and knowledge of etiological microbial agents) and prediction of clinical outcome (35-38). Therefore, the focus in primary care is not on finding the causative agent but on the assessment of the risk of a complicated course.

The current strategy aims at identifying patients with pneumonia or lower respiratory tract infection with an increased risk for a complicated course (39). This strategy focuses on the evaluation of the intensity of the host inflammatory response. In this line of reasoning, mildly ill patients likely have limited inflammation only, and thus a small chance of having extensive tissue involvement and significant pneumonia, and by consequence, a favourable outcome. In these patients, lower respiratory tract infection is caused most

often by a virus, and withholding antibiotic treatment does not pose a risk. On the other side of the spectrum, severely ill patients are likely suffering an extensive inflammatory response, have a bigger chance that the infection is caused by bacterial pathogens, and are at an increased risk of a complicated and unpredictable course of pneumonia. These patients should receive antibiotic treatment. Obviously, those in between, i.e., the group of patients that appear ill but are not acutely, severely ill, provide the clinician with the biggest challenge. From these moderately ill patients, it is less clear who will go on to develop a potentially life-threatening infection and would benefit from antibiotic treatment, and who will not. Even in this group, the majority of patients will have a viral cause of acute respiratory tract infection and self-limiting disease. Treating all of the patients in this intermediate group with antibiotics, therefore, would result in unnecessary side-effects, promote antimicrobial resistance, and results in high costs.

Unfortunately, for a diagnosis of pneumonia (most often defined as new infiltrate on the chest X-ray), taking a medical history and performing a physical examination lack sensitivity and specificity (40, 41). In most instances, taking a chest X-ray in patients with an acute respiratory tract infection is neither feasible nor cost-effective, and many general practitioners (GPs) rely on readily available point-of-care testing of biomarkers to help guide their therapeutic decisions. To improve diagnosis and help making therapeutic decisions the general practitioner (GP) can order a chest X-ray or rely on readily available C-reactive protein (CRP) point-of-care testing.

First, the chest X-ray is considered by many the gold standard in defining pneumonia. However, a chest X-ray in outpatients does not improve outcome, and therefore this is not routinely recommended for patients attending their GP with suspicion of acute respiratory tract infection or community-acquired pneumonia (42, 43). In addition, in general, primary care patients must be referred to hospital for an X-ray of the chest, making this a far from attractive first-line diagnostic test. Still, in some patients, a definite conclusion on the presence or absence of pneumonia (as determined by chest X-ray) would help physicians in decision making. For example, in patients not improving on empirical antibiotic treatment or in moderately ill patients with specific underlying diseases, a chest X-ray could help guide the general practitioner in deciding about antibiotic treatment, a wait-and-see policy, or prompt referral to a hospital. Until now, research into the effects and the effectiveness of chest X-rays by the general practitioner for subgroups of patients with an acute lower respiratory tract infection is lacking.

Secondly, CRP point-of-care tests are available. CRP is a biomarker of inflammation, and the results of the point-of-care test are directly available at the time and place of patient care. Studies have shown that a low CRP (< 20 mg/l) can with reasonable certainty ex-

clude pneumonia, irrespective of medical history, comorbidity, and findings on physical examination, while an elevated CRP (> 100 mg/l) dramatically increases the chance of pneumonia warranting antibiotic treatment (44, 45). A meta-analysis ascertained that even when clinical variables are taken into account, the CRP test can help confirm or exclude the presence of pneumonia (46). Thus, this inflammatory biomarker can help GP decision making in daily practice. In a large European cohort, CRP added to clinical signs and symptoms improved assessment of presence or absence of pneumonia in 29% of patients with acute cough (45). However, these are not necessarily the patients suspected of having pneumonia and the ones for whom diagnostic challenges remain. Although the CRP test helps to fill in some of the grey areas of patients with sickness of intermediate severity, it is not surprising that in turn, this new assay creates a new area of uncertainty. In particular, for moderately ill patients with an acute respiratory tract infection and intermediate CRP levels (between 20 and 100 mg/l), evidence-based practice guidelines are lacking. Furthermore, studies that evaluated whether the CRP point-of-care test reduced the number of antibiotic prescriptions showed variable results (47, 48).

There is a continuous search for an optimal biomarker which will distinguish unequivocally viral from bacterial causes of infection and potential inadvertent outcomes from favourable ones, and thus, provide a holy grail on guidance for antimicrobial therapy. So far, besides CRP, procalcitonin (PCT) and mid-regional pro-adrenomedullin (MR-proADM) have shown some promise as biomarkers for the severity of inflammation. Strong evidence which of these markers best predicts outcome in patients with an acute respiratory tract infection is however still lacking. The evidence-based use of these types of additional diagnostics is not established and many worries remain about inappropriate use of these tests that rapidly become more popular. A critical assessment of the current use of these additional diagnostics in daily general practice, the interpretation, and consequences of the test results, will help researchers and clinicians to identify knowledge gaps. Respiratory tract infections are frequently seen in primary care; therefore evidence-based guidelines regarding the use of additional diagnostics are urgently needed, in particular for use in moderately ill patients.

Detection of lower respiratory tract infection at the emergency department

To determine the presence or absence of pneumonia in the setting of the emergency department is less challenging than in primary care. The prevalence of pneumonia among coughing patients at the emergency department (i.e., pre-test chance) is much higher than among primary care patients, and chest X-ray and other radiological diagnostics are readily available at the emergency department. Also, a choice can be made of various microbiological diagnostic tests, tailored to an individual patient`s need (49).

More challenging are the treatment decisions. As physicians at the emergency department cannot determine causative agent on the spot, empirical treatment is – just like in primary care – guided by epidemiological setting (e.g., specific exposure) and severity of disease (i.e., host immune response) (50, 51). The pneumonia severity index has been developed to stratify patients according to prognosis and to guide empirical treatment (50). The studies into predicting pneumonia severity also found that the less severely ill patients, with a limited host inflammatory response, have only a marginal 30-day mortality (50, 51). Thus, these patients can safely be treated with small spectrum antimicrobial therapy in combination with starting microbiological diagnostic tests aimed to adjust the empiric treatment if necessary, and secure follow up. More severely ill patients with an abundant inflammatory response, have an increased 30-day mortality risk and should, therefore, be treated with broad-spectrum antimicrobial therapy. In this group of patients, antimicrobial therapy alone might not be enough. Also, the timing of antimicrobial therapy is important and, without interfering with the effect of the antimicrobial therapy, interventions aimed at attenuation of the inflammatory host response may be necessary, as this can cause collateral damage.

Timing of initiation of antimicrobial therapy at the emergency department

Timely administration of antimicrobial treatment is important to obtain the optimal effect. Early and prompt treatment will prevent microbes from replicating, thereby preventing an even more extensive inflammatory response. Indicators of timing as the door-to-needle time have been used to improve timely administration of appropriate antibiotic treatment. This door-to-needle time is derived from acute ischemic events where timely administration of reperfusion therapy could save organ tissue (52). In patients with pneumonia, early initiation of treatment has been shown to improve outcome (53). Still, administration of antibiotics inappropriate for the etiologic pathogen (e.g., lacking activity against the microorganism) is, however, the strongest predictor for mortality in patients with severe infection (54). Therefore, a short assessment time at the emergency department is essential to minimize the risk of potential harm to patients who eventually did not have a (bacterial) infection, and to determine the adequate empiric antimicrobial treatment if needed (55). If the presence of bacterial infection is likely, the differential diagnosis of possible etiologic microorganisms must be made and the benefit of antimicrobial therapy options considered, and appropriate antimicrobial treatment should be started as soon as possible.

In patients with severe bacterial infections, early treatment is better than late treatment, but late treatment is still better than an ill-directed or no treatment. In contrast, in influenza virus-infected patients in outpatient settings, the time window for treatment with

antiviral neuraminidase inhibitors seems very small, and it was shown that treatment of healthy volunteers ≥48 hours after first symptoms had no added benefit over no treatment (56, 57). Patients hospitalized for influenza may represent a distinct group with continuing viral replication and an extended therapeutic window. For instance, younger hospitalised patients with H1N1pdm09 influenza virus infection had reduced mortality when neuraminidase inhibitor treatment was initiated within 48 hours after the start of symptoms, but this effect remained, although less pronounced, until treatment initiation within five days after symptom onset (58).

In patients at the emergency department, who are elderly, frail, or immunocompromised and at high risk for developing complications, this time window for antiviral treatment is not clear. In daily practice, the majority of these patients present to a hospital with symptoms that started more than 48 hours earlier (58, 59). Evidence for benefits of neuraminidase inhibitor treatment of these patients admitted with seasonal influenza is scarce and is often extrapolated from studies in other patient groups. The benefit of late initiation of treatment (that is >48 hours after symptom onset) has been questioned (60, 61). In addition, negative reporting about the neuraminidase inhibitor oseltamivir has further increased the uncertainty of oseltamivir´s potential benefit (62). The uncertainty about the effectiveness of oseltamivir treatment in patients admitted with influenza virus infection remains a daily challenge during the yearly influenza season.

Attenuation of host inflammatory response to improve outcome

What can we do, besides early initiation of antimicrobial therapy in patients with severe pneumonia (i.e., characterized by an intense inflammatory response), to attenuate inflammatory response without interfering with the antimicrobial properties of such response? Adjunctive anti-inflammatory therapeutic options are being studied (63). For community-acquired pneumonia, macrolides have been proposed to have a positive immune modulatory effect by enhancement of the antibacterial effect of neutrophils and by quashing the immune response after bacterial killing, potentially improving outcome (64, 65). However, this in vitro effect was not observed in a clinical trial in which β-lactam monotherapy was found to be non-inferior to macrolide with β-lactam combination therapy (5).

Corticosteroid therapy in community-acquired pneumonia would improve short term outcome measures but has a large number of side effects (66, 67). Consequently, primary and secondary care guidelines do not recommend to add corticosteroid or other immunosuppressive treatments to the therapy of patients with community-acquired pneumonia. However, in other life-threatening infections such as pneumococcal meningitis, dampening the host inflammatory response has been recognized as an important adjunct treatment. Most treatment protocols dictate that dexamethasone is given to patients with

pneumococcal meningitis before an antibiotic is administered. This approach has been shown to decrease the inflammatory response and to improve treatment outcome (68).

Another approach would be to limit the initiation of the host immune response, i.e., to decrease the quantity of immune-reactive components that are released following the start of antimicrobial treatment. Some research into this approach has been done in pneumococcal infections. *Streptococcus pneumoniae* is the most frequent bacterial causative agent of pneumonia, and pneumococcal infections have substantial morbidity and mortality, mostly driven by an intense host inflammatory response (69). As in other infections with Gram-positive bacteria, this inflammatory response is primarily induced by the release of large quantities of immune-reactive bacterial cell wall components (e.g., lipoteichoic acid) and intracellular proteins (70). Specific antibiotics that lyse the pneumococci enhance this release. Previous in vitro and animal studies, showed a decreased lipoteichoic acid release and subsequent dampened inflammatory response when *Streptococcus pneumoniae* is killed with non-lytic antibiotics, that is rifampicin as opposed to for instance β-lactams (71, 72). To our knowledge, studies in humans to evaluate this effect on inflammatory response and outcome are currently lacking.

Moreover, the H1N1 influenza pandemic gave insight into a rare but potentially lethal inflammatory complication of flu: Acute Respiratory Distress Syndrome (ARDS) (73, 74). ARDS risk factors and pathophysiological mechanisms are currently investigated. ARDS is an inflammatory response with epithelial and alveolar cell damage leading to bilateral opacities on chest radiograph with marked hypoxia occurring within seven days after a clinical insult (75, 76). Since the 2009 H1N1 influenza outbreak, numerous reports appeared indicating that influenza virus infection may, in rare cases, cause ARDS (73, 77). Of note, ARDS can also occur after many other unrelated triggers, for example, sepsis, trauma, inhalation of exogenous toxins, or major surgery (78). Likely, ARDS is caused by the occurrence of several, sequential hits to the lung (79, 80). Little knowledge exists about whether such sequential hits are relevant clinically, for instance, whether elective surgery would lead to a higher percentage of ARDS cases during seasons with respiratory viruses circulating. In this respect, it is of interest that it was found that different viruses are associated with ARDS in critically ill patients (81, 82).

In conclusion, care for patients at risk for an acute respiratory tract infection can likely be optimized by improved application of vaccination strategies, early detection of specific etiologic microorganisms (or at least distinguish a viral from bacterial cause), adequate assessment of the host immune response, and attenuation of an excessive host inflammatory response.

OUTLINE OF THIS THESIS

The current thesis aims to optimize care for patients at risk for or with an acute respiratory tract infection, in several clinical domains, with a focus on prevention, early detection of outbreaks, early diagnosis of lower respiratory tract infection, and strategies to attenuate the inflammatory response and improve clinical outcome in these patients.

In **chapter 2**, the ICARES (Integrated Crisis Alert and REsponse System) project is described, a new automated real-time tool for the detection of clusters of infectious diseases. Besides respiratory tract infections we also analysed two other infectious diseases with the ICARES project: infectious hepatitis and meningitis/encephalitis.

Chapter 3 focuses on the difference in severe acute respiratory infection (SARI) surveillance in secondary care and influenza-like illness (ILI) surveillance in primary care. These surveillance systems are important to detect and monitor the yearly outbreaks**.** The added value of SARI surveillance upon ILI surveillance is discussed.

The use of additional diagnostics by general practitioners in patients with an acute respiratory tract infection is described in **chapter 4**. Use of C-reactive protein for acute respiratory infections is well established in current guidelines. On the contrary, the use of X-rays of the chest is only briefly mentioned in guidelines, and usually without clear indications. We evaluate the current clinical use of both diagnostics and discuss ways to improve strategies.

Chapter 5 describes a cohort of patients with an acute respiratory tract infection for whom their general practitioner orders a chest X-ray. With this cohort, we determine predictive clinical parameters and biomarkers for the presence of pneumonia.

Vaccination is vital in preventing respiratory infections in the general population. Although most agree on the urgent need for an improved, more effective influenza vaccine, currently it is all there is available to prevent influenza. In the healthy and various subgroups of patients, influenza vaccination has shown effectiveness, though limited. Anecdotal reports about side effects withhold caregivers from vaccinating patients who would benefit from influenza vaccination. In **chapter 6**, we describe the absence of excessive immune-related adverse events of influenza vaccination in lung cancer patients treated with immunotherapy. In **chapter 7**, we discuss influenza vaccination in health care workers during the severe influenza season 2017/2018.

The burden of influenza virus infection in three large hospitals in the Netherlands and the analysis of the treatment effect of oseltamivir are topics in **chapter 8**. Can we prevent mortality and in-hospital complications by initiating treatment at admission?

Chapter 9 deals with a complication of influenza virus infection: pneumococcal pneumonia. The PRISTINE (Pneumonia treated with RIfampicin aTtenuates Inflammation) study is the first pilot clinical trial in humans to determine the feasibility of adding rifampicin to standard treatment with β-lactams in patients with community-acquired pneumonia. This combined treatment is done to reduce the release of pro-inflammatory bacterial compounds within the first hours of therapy, and to thereby attenuate the host inflammatory response and improve outcome.

Pneumococcal pneumonia is an obvious complication of influenza virus infection, but there might be more complications related to influenza. As most influenza infections are asymptomatic, we hypothesized that asymptomatic influenza infection in cardiac surgery patients is a risk factor for postoperative Acute Respiratory Distress Syndrome (ARDS). The results of an investigation into the prevalence of ARDS after elective surgery within and outside the influenza season are made available in **chapter 10**.

In **chapter 11**, the findings of this thesis are summarized and discussed in light of the literature and future directions of research.

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