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Advances in clinical development for vaccines and therapeutics against respiratory virus infections

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CHAPTER 1

INTRODUCTION

The evolutionary origin of viruses is unclear, although there appears to be consensus that they originate from DNA or RNA of living organisms. In the beginning of the 20th century the Dutch scientist Beijerinck demonstrated the existence of viruses and the first images of viruses appeared with the availability of electron microscopy in the 1930s.[1,2] Since the second half of 20th century many (thousands) viruses have been identified and are commonly named by the name of the organ/system that is affected most. This thesis focusses on respiratory viruses, which have probably been around since time immemorial. Respiratory viruses can be transmitted through excreted droplets, exhaled aerosols or contact with contaminated surfaces.[3] These viruses may infect the respiratory epithelial cells of the nose, throat and sometimes also the lower respiratory tract.[3,4] Respiratory viruses can cause various respiratory and systemic symptoms such as: sneezing, coughing, rhinitis, throat ache, nasal congestions, fever, malaise, myalgia. It is however not possible to discriminate causative pathogens based on clinical presentation alone because symptoms are overlapping and non-specific. Molecular diagnostics, such as multiplex real-time polymerase chain reaction (PCR), are therefore needed to reliably detect the causative agent.[5] Respiratory viruses have a wide spectrum of clinical disease: from asymptomatic infection and upper respiratory complaints (common cold) to acute lower respiratory disease with respiratory insufficiency, systemic inflammatory response syndrome and may even lead to death in individuals at risk.[6-9] Respiratory virus infections occur in persons of all ages and re-infections with the same virus species occur throughout an individual's lifetime.[10] This is because natural respiratory virus infection does not confer lasting sterile immunity. Respiratory viruses have various mechanisms of host immune evasion and virus surface antigens can change relatively quickly through evolutionary pressure.[11,12]

Most respiratory virus infections are self-limiting with only mild symptoms in healthy immunocompetent adults, however, some viruses can cause severe disease in specific subpopulations. Respiratory syncytial virus (RSV) and influenza virus are two RNA viruses that have been historically associated with substantial mortality and hospitalization rates.[9,13] In developed countries the mortality in adults aged 65 years or older has been estimated around 21 and 15 per 100,000 individuals for seasonal influenza and RSV, respectively.[9] Mortality rates in low-to-middle income countries are expected to be even higher.[14] Both viruses are associated with excess mortality in elderly individuals (>65 years), chronically ill and children, but RSV especially poses a great risk to young infants.[9] RSV can cause severe lower respiratory tract infections (bronchiolitis, bronchospasms, pneumonia and respiratory failure) and is a leading cause of hospitalization and death of infants, worldwide.[15,16] Influenza can cause serious complications such as secondary pneumonia and exacerbations of chronic lung diseases.[17,18] Children (younger than 5 years), elderly and chronically ill are at increased of developing such complications.[19]

Severe disease can also occur in seemingly healthy individuals if a novel antigenic virus variant occurs for which there is no pre-existing immunity. An example is the devastating 1918 influenza pandemic caused by the H1N1 virus that contained genes of avian origin for which there was pre-existing immunity in the human population.[20] The estimated death-toll of this pandemic is estimated to exceed 20 million people.[21] In the last decades novel highly pathogenic corona viruses emerged from zoonotic spillover, such as Severe Acute Respiratory Syndrome (SARS, 2003) and Middle East Respiratory Syndrome (MERS, 2012).[22,23] At the end of 2019, the fear of a new pandemic suddenly became reality when the novel human coronavirus SARS-COV-2 was first identified following a cluster of pneumonia casus of unknown etiology in the Wuhan region of China.[24] Infection rates grew exponentially and Corona Virus Diseases 2019 (COVID-19) was declared a pandemic on March 11th 2020 by the World Health Organization (WHO) and resulted in the largest public health crisis of this century.[25] Infection with SARS-COV-2 leads to a wide spectrum of disease: from asymptomatic and mild flu-like illness to serious complications such as septic shock, pneumonia, acute respiratory distress syndrome and cardiovascular events. The WHO currently estimates that there have been more than 600 million confirmed cumulative cases and over 6 million deaths.[26] In addition, COVID-19 has generated a substantial financial burden on health care systems and the general population.[27] During the writing of this thesis, COVID-19 still has a large impact on health care and society as a whole.

Historically, respiratory syncytial RSV and influenza have received the most research interest of all respiratory viruses due to their high global disease burden. Research into therapies and vaccines against these viruses have been ongoing for almost a century, ever since the first isolation of influenza in 1933.[28] One of the largest scientific breakthroughs was the development of the influenza vaccine in the 1940s.[28] However, shortly after its

discovery it became apparent that vaccines against influenza needed to be updated annually. This became painfully clear in the influenza epidemic of 1947. The vaccine failed almost completely due to marked (intrasubtypic) antigenic variation in the prevalent influenza strain (H1N1) of 1947.[29] Since then, there has been an ongoing endeavor to adapt, re-formulate and re-administer influenza vaccines annually to keep up with the evolution of the influenza virus. Modern seasonal influenza vaccines are tri- or quadrivalent, they contain antigens derived from multiple virus strains (2 influenza A subtypes and 1 or 2 B lineages). Unfortunately, current vaccines are far from perfect; their effectiveness is variable and partly depends on the match of the vaccine strain with the most prevalent circulating strain of that particular year.[30] The overall effectivity of influenza vaccines in adults is modest: 59% for inactivated parental vaccines and 53% for live-attenuated mucosal vaccines).[31] In addition, current influenza vaccines do not sufficiently prevent virus transmission.[32,33] Preventing transmission of influenza virus throughout the population would be highly desirable from a public health perspective.

Current seasonal influenza vaccines are designed to elicit serum antibodies to the highly antigenically variable and immunodominant heads of the hemagglutinin (HA) protein. Immunity induced by these vaccines is specific for influenza strains that match the vaccine antigen and generally lack efficacy against other strains.[34] The development of a broadly protective 'universal' influenza vaccine has been on the research agenda for decades. A universal influenza vaccine would also serve as the best defense against an emerging pandemic influenza strain. Such a vaccine might target more conserved influenza virus epitopes to induce immunity against multiple strains.[35,36] Recently, new universal flu candidates have entered clinical development with some promising preliminary results.[37] However, until a universal vaccine is available, efforts should also be made to improve immunogenicity and cross-reactivity of currently available seasonal influenza vaccines, especially in populations at risk for serious complication. New adjuvants could increase the immunogenicity of current and investigational vaccine technologies while development of improved mucosal vaccine platforms could elicit local immunity (next to a sufficient systemic antibody response).

Therapeutic and non-vaccine prophylactic compounds against influenza are scarce. For influenza there are a handful of antivirals authorized by European Medical Agency (EMA). The majority belong to the class of neuraminidase inhibitors (NAIs), such as oseltamivir and zanamivir. By inhibiting neuraminidase – a glycoprotein with enzymatic activity conserved within all influenza viruses – the release of virions from host cells is diminished.[38,39] Although the mechanism of action is appealing, the clinical effects are modest with a reduction of the time of symptom alleviation in adults by less than day.[40] Treatment initiation is recommended as soon as possible after illness onset, as clinical benefit has been shown to be highest within the first days after onset.[41,42] A second group of authorized antivirals consist of viral ion channel M2 inhibitors (such as amantadine and rimantadine). These antivirals are only effective against influenza A strains and widespread resistance has been reported.[42,43] The novel cap-dependent endonuclease inhibitor baloxavir marboxil did not improve time to symptom alleviation compared to oseltamivir in uncomplicated influenza.[44] Large scale use of antivirals has been debated due to their cost-effectiveness ratio's, associated adverse events and the development of antiviral drug resistance.[40,45,46] Advances in effective antivirals that reduce mortality and disease progression are highly needed, especially considering that antiviral therapies are the first-line of defense during a influenza pandemic, when vaccines are still in development or supply is still insufficient.

In contrast to influenza, there is no vaccine available yet for RSV and only very few authorized anti-infectious compounds. Palivuzimab, a humanized IgG_1 monoclonal antibody (MAB) targeting the surface fusion (F) protein, is the only compound authorized in the European Union for (passive) prophylaxis.[47] Its use is currently restricted to children <2 years with a high risk of severe RSV disease (such as preterm infants). Unfortunately, the high cost of passive immunization with palivizumab and repeated intramuscular administration limits widespread global use. This applies especially to low- and middle-income countries where disease burden and RSV-related mortality are highest.[48]

Attempts to develop a safe and effective vaccine for RSV have been ongoing for decades. A major setback was the unpredicted occurrence of vaccine-enhanced disease in an RSV trial with formalin-inactivated RSV (1967).[49,50] Children were not protected and subsequent RSV infection led to worsening of respiratory symptoms, hospitalization of many children and the dead of two.[50,51] To mitigate the risk of vaccine enhanced disease,

new vaccines-candidate now have to show compelling and robust pre-clinical safety and immunogenicity data before clinical testing.[52] In addition, safety and immunogenicity data must first be obtained from healthy adults, before exposure to non-naïve children and subsequently immune-naïve infants.[52] Due to an improved molecular understanding of RSV and innovative biotechnologies, the vaccine pipeline has been filled with various new platforms.[53] Hopefully, one of these candidates will succeed to bring forth the first RSV-vaccine soon.

The previous paragraphs illustrate that despite decades of research there are still substantial knowledge gaps that hinder the development of safe and (more) effective vaccines and therapeutics for influenza and RSV. Aware of the difficulties of the development of vaccines and therapeutics for respiratory viruses, the medical community was forced to tackle the COVID-19 pandemic. With no effective treatments or vaccines against coronaviruses, investigators and regulators were challenged with the enormous task to expedite development of vaccines, anti-infectious and disease modifying agents. This required *drug repurposing* of existing authorized compounds with potential antiviral or immunomodulatory properties (e.g. hydroxychloroquine and chloroquine) and investigating promising antiviral candidates in late stage clinical development for other diseases (e.g. remdesivir).[54-57] As more data became available about SARS-COV-2 genome, structural biology and pathophysiology, novel compounds were to be developed and brought from bench-to-bed at an unprecedented pace. Both pre-existing and experimental vaccine platform technologies were used as a base to develop COVID-19 vaccines.[58]

To allow for rapid development and large-scale availability of vaccines and therapeutics, a paradigm shift in drug and vaccine development was needed.[59,60] Developing novel anti-infectious agents and vaccines from discovery to widespread public availability takes up to 10 years on average.[61] Traditionally, drug development is an iterative process characterized by different sequential phases, starting at early discovery of compounds through pre-clinical testing, clinical development (sequential phase I, II and III testing) leading to application of authorization, registration and finally marked introduction. To expedite development during a pandemic, the developmental phases needed to overlap to reach the finish-line earlier (*Figure 1*). To accelerate development time, early clinical studies may be performed in parallel to pre-clinical studies, provided that there is robust toxicology and clinical safety data from similar pharmaceutical products derived from the same platform technology.[62] Phase I and II clinical trials may be combined in larger study protocols as long as there are staggered dosing approaches and rigorous safety monitoring.[63-65] Timely availability also depends on regulators prioritizing review procedures by giving compounds for COVID-19 'emergency fast-tracks' designations.[66] Close collaboration and early discussions between investigators and regulators is needed to provide pivotal clinical data in the most efficient manner. The COVID-19 pandemic has revealed that innovation is not only needed on a level of basic science and drug development but also clinical trial conduct and regulations.

Necessity became the catalyst of innovation throughout the COVID-19 pandemic. The development of vaccines and therapeutics during the pandemic crisis required a collective effort from the medical and life science community. Currently, over 4000 interventional clinical studies have been registered for COVID-19 (ClinicalTrials.gov). Before the COVID-19 pandemic, data on attrition rates of vaccines and anti-infectious therapies showed that the vast majority of these compounds failed to reach market authorization (probability of market entry of vaccines was estimated to be 1.8% in 2014).[67] Nonetheless, vaccines and therapies were successfully developed for COVID-19 and they mostly relied on innovative technologies that were already in development years prior to the onset of the pandemic. The first vaccines became available approximately a year after the discovery of SARS-COV-2 and without compromising on safety. The first vaccines were based on novel delivery platforms such as mRNA and viral vectors. The therapeutic arsenal for COVID-19 has expanded significantly and currently includes immunomodulatory compounds, small molecule antivirals and monoclonal antibodies. However, due to the emergence of novel variants of concern and ongoing transmission, vaccines need to be adapted and the threat of resistance against therapies remain. Innovation is therefore still highly needed and ongoing.

AIM AND OUTLINE OF THIS THESIS

This thesis aims to assess several innovative novel compounds in clinical development for three of the most impactful respiratory viruses: RSV, Influenza and SARS-COV-2. A summary of biological and clinical characteristics of RSV, Influenza and SARS-COV-2 is provided in *Table 1*. Next to pharmacological

innovations in clinical development, this thesis also explores novel approaches for clinical trial conduct during a pandemic and provides means for regulators and investigators to accelerate early clinical development in pandemic situations. The studies described in this thesis took place before the COVID-19 pandemic (*Section 1 and 2*) and partly during the pandemic (*Section 3*).

In *Section 1 Respiratory Syncytial Virus* a novel live-attenuated RSV vaccine candidate lacking the surface G-protein is assessed for the first time in humans. The safety profile of this genetically modified intranasal vaccine should first be investigated in healthy adult volunteers who have been previously exposed to RSV before testing in the target population (naïve infants). To better assess viral shedding he immunogenicity (functional effect) we performed an observational study to examine the distribution of neutralizing RSV antibodies in the envisioned phase I adult study population (*Chapter 2*). It was hypothesized that a lower titer of antibodies could potentiate immune effects and allow for viral replication. Based on this study an eligibility criterion was defined for the randomized controlled clinical trial investigating the safety, immunogenicity and viral shedding of intranasal administration of the RSV vaccine candidate (*Chapter 3*).

Section 2 Influenza Virus described the use of a novel bacteria-like particle (BPL) as adjuvant to increase the immunogenicity of intranasally administered seasonal inactivated trivalent influenza vaccine (*Chapter 4*). This randomized controlled clinical trial explored three increasing dose levels of the adjuvant in healthy adults. The elderly population is known to be at risk of developing influenza related complications but tend to have generally lower vaccine-induced immune responses. The trial concluded with the testing of the most immunogenic dose of the adjuvant in individuals aged 65 years and older (target population).

Section 3 SARS-COV-2 and clinical development during pandemics starts with the development of a novel therapeutic for COVID-19 (*Chapter 5*). Ensovibep – a tri-specific DARPin molecule that binds to the SARS-COV-2 spike protein – was administered for the first time in patients with mild-to-moderate COVID-19 in an outpatient settings. This study served as a feasibility study in the clinical development trajectory of ensovibep, but the study was designed to also gain early clinical insight of the patient safety profile, pharmacokinetics and immunogenicity of two envisioned dose levels of ensovibep.

Chapter 6 investigates the immunomodulatory effect of hydroxychloroquine, a drug that was repurposed for COVID-19 and widely used during the first months of the pandemic. Hydroxychloroquine showed *in vitro* antiviral activity against SARS-COV-2 and is a known immunomodulatory drug. It was hypothesized that the immunosuppressive action of hydroxychloroquine could prevent the adverse immune reaction in severe COVID-19. Large randomized controlled efficacy trials later showed no clinical benefit of hydroxychloroquine for COVID-19. The reversed translational study (*from bed-to-bench*) presented in *Chapter 6* assessed and quantified the immunomodulatory effects of hydroxychloroquine on primary human immune cells, both *in vitro* and *ex vivo,* in a randomized clinical trial.

The last two chapters describe innovative approaches to clinical trial conduct and regulations during a pandemic. A novel approach to conducting vaccine field trials is introduced in *Chapter 7*. Through epidemic modelling and clinical trial stimulations a *hot spot* identification and recruitment strategy is compared to the traditional *wait-and-see* approach commonly used in phase III vaccine field trials. *Section 3* concludes with a pragmatic overview of recommendations that may facilitate accelerated development of early phase clinical trial in a pandemic crisis (*Chapter 8*).

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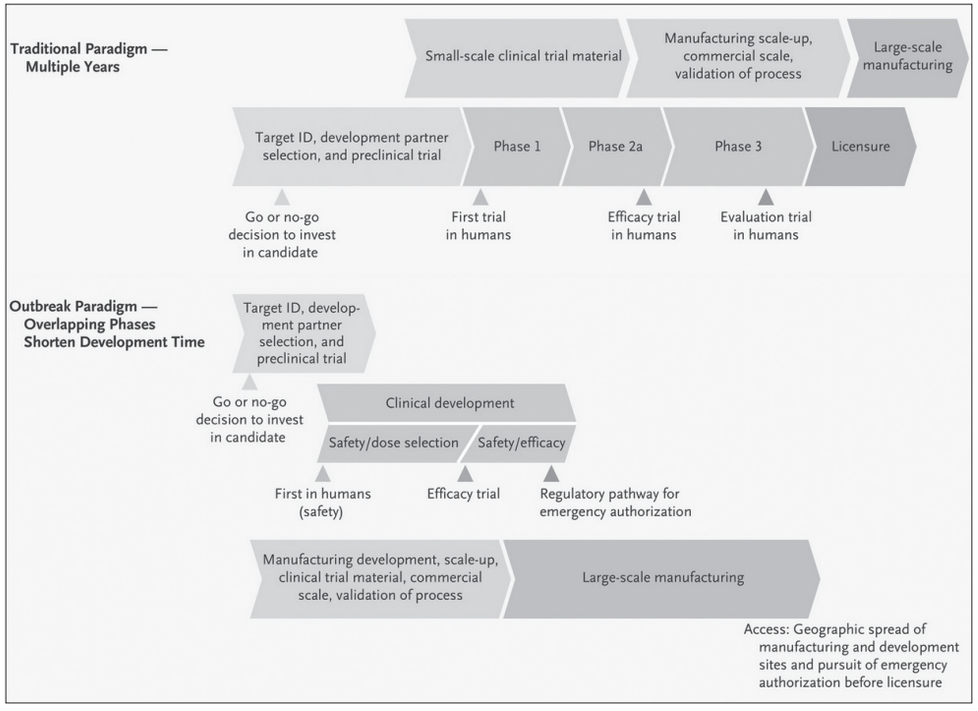
TABLE 1 SUMMARY OF VIRUS CHARACTERISTICS.

	Respiratory Syncytial Virus	Seasonal Influenza	SARS-CoV-2
Genome size (kilobases)	~ 15.2	~ 13.5	~ 29.9
Genetic material	Negative–sense RNA, non–segmented	Negative–sense RNA, segmented	Positive–sense RNA, non–segmented
Incubation time	4–8 days	1–4 days	4–5 days
Patients at risk of severe disease or complications*	**Children**: < 5 years (especially infants < 6 months), born < 35 weeks gestation, congenital heart and lung diseases, immunocompromised **Adults**: chronic cardiopul–monary disease, function–al disability, nursing home residents	Children < 5 years, adults ≥ 65 years, pregnant or 3 weeks postpartum, nursing home residents, diabetes mellites and various chronic co–morbidities	Age ≥ 65 years, chronic long, cancer, kidney and cerebrovascular diseases, immunocompromised, body mass index ≥ 30, physical inactivity, smoking
Major antigens	Fusion (F) protein, attachment (G) protein	Hemagglutinin (HA) and neuraminidase (NA)	Spike (S) protein
Vaccine availability and platform technology	No vaccine currently available	Multivalent inactivated and live–attenuated vaccines	RNA, viral vector, inactivated, protein subunit
Available therapies	Passive immune prophylaxis (palivizumab) for high risk infants	Antivirals: neuraminidase inhibitors, adamantanes, baloxavir marboxil	Various: monoclonal antibodies, small molecule antivirals, immunomodulators, dexamethasone, convalescent plasma

**Clinically relevant risk factors, however, not intended as an exhaustive list of all known risk factors for severe disease or complications.*

FIGURE 1 DIFFERENCE BETWEEN TRADITIONAL VACCINE DEVELOPMENT AND DEVELOPMENT USING A PANDEMIC PARADIGM.



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