Advances in clinical development for vaccines and therapeutics against respiratory virus infections
J.L. van der Plas

Citation
Advances in clinical development for vaccines and therapeutics against respiratory virus infections. (2023, September 26). Advances in clinical development for vaccines and therapeutics against respiratory virus infections. Retrieved from https://hdl.handle.net/1887/3642223

Version: Publisher's Version
License: Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from: https://hdl.handle.net/1887/3642223

Note: To cite this publication please use the final published version (if applicable).
**FIGURE 7** **IN VIVO HCQ DID NOT AFFECT T AND B CELL PROLIFERATION.** PBMCs were stained with CTV and stimulated for 5 days with 5 μg/mL PHA for T cell proliferation (a), or 5 μg/mL anti-CD40 mAb + 2.5 μM CpG B for B cell proliferation (b). Proliferation was measured by flow cytometry.

**A**

- **CD4**
  - Proliferation (%) over time (days)
  - Data is shown as mean ± SD. Dotted vertical lines indicate HCQ dosing times.

**B**

- **CD8**
  - Proliferation (%) over time (days)
  - Data is shown as mean ± SD. Dotted vertical lines indicate HCQ dosing times.

**C**

- **CD19**
  - Proliferation (%) over time (days)
  - Data is shown as mean ± SD. Dotted vertical lines indicate HCQ dosing times.

**CHAPTER 7**

**ACCELERATING VACCINE TRIAL CONDUCT IN A PANDEMIC WITH A HOT SPOT-BASED INCLUSION STRATEGY USING**


doi: 10.1111/cts.13104

SUPPLEMENTARY FIGURES AND TABLES

All mentioned supplementary figures and tables in this chapter can be found on the corresponding website by scanning this QR code.
Abstract

Clinical development of vaccines in a pandemic situation should be rigorous but expedited to tackle the pandemic threat as fast as possible. We explored the effects of a novel vaccine trial strategy that actively identifies and enrolls subjects in local areas with high infection rates. In addition, we assessed the practical requirements needed for such a strategy. Clinical trial simulations were used to assess the effects of utilizing the so-called ‘hot spot strategy’ compared to a traditional vaccine field trial. We used pre-set parameters of a pandemic outbreak and incorporated realistic aspects conducting a trial in a pandemic setting. Our simulations demonstrated that incorporating a hot spot strategy shortened the duration of the vaccine trial considerably, even if only one hot spot was identified during the clinical trial. The active hot spot strategy described in the paper has clear advantages compared to a ‘wait-and-see’ approach that is used in traditional vaccine efficacy trials. Completion of a clinical trial can be expedited by adapting to resurgences and outbreaks that will occur in a population during a pandemic. However, this approach requires a speed of response that is unusual for a traditional phase III clinical trial. Therefore, several recommendations are made to help accomplish rapid clinical trial set-up in areas identified as local outbreaks. The described model and hot spot vaccination strategy can be adjusted to disease-specific transmission characteristics and could therefore be applied to any future pandemic threat.

Introduction

The viral genome of the causative pathogen of coronavirus disease 2019 (covid-19), severe acute respiratory syndrome-coronavirus 2 (sars-cov-2) was published on National Center for Biotechnology Information (ncbi)/Gen Bank on January 11, 2020, about 2 weeks after the identification of the first patient with this disease that has since overwhelmed the world. The subsequent development and marketing approval of several vaccines for sars-cov-2, took approximately a year from the identification of the viral genome. This speed of development is clearly extraordinary and has no precedent in the development of any therapeutic or preventive intervention, using modern quality standards. However, in the course of this year, 1.5 million people died and countless others became ill and the personal and economic consequences were dire. Any strategy to reduce the development time of a vaccine, even by days or weeks, would be of enormous benefit. This realization has led to several initiatives to speed up the process that subsequently clearly paid off. However, the question remains whether further gains could be made by better preparedness for a new pandemic, that will without any doubt occur again.

After identification and construction of the vaccine compound, the development trajectory of a vaccine moves from the establishment that the prophylactic intervention works to that it helps. By this we mean that for a vaccine to work, it first needs to be established that vaccination leads to a potent and specific immunogenic response. This can be assessed relatively quickly in clinical trials with a relatively small number of subjects. Indeed, the first studies indicating initial safety and immunogenicity of vaccines appeared approximately 6 months after a vaccine candidate was identified. Although it could be argued that this is about the maximum speed possible for this phase, we have identified several bottlenecks that could be addressed to speed up clinical development.

In the case of a novel pathogen it cannot be assumed that a neutralizing immune response automatically prevents clinical disease and the regulatory position about this is unequivocal. Therefore, the establishment that a vaccine helps, in that it successfully prevents disease or even transmission, requires evidence from large field studies. These trials have the primary objective to establish efficacy, but also gather sufficient data on vaccine safety and therefore require a size of approximately 15,000-20,000
volunteers vaccinated with the active compound to detect rare side effects that occur with a frequency of about 1:10,000 with reasonable certainty. To put it concisely, thousands of people are vaccinated in a short period and investigators wait to see how many volunteers become infected in the group receiving the vaccine compared to the placebo (or other comparator) group. However, such trials will only reliably demonstrate efficacy when the number of infections in the studied population is sufficiently high. Consequently, these trials will not reach the efficacy objective when the caseload is low. In a pandemic, this will inevitably happen after an outbreak has been identified, as governmental control interventions will be put in place to prevent further transmission, change population behavior and reduce the caseload.

When trials are executed in areas with a less than expected caseload, the trial will take much longer to complete, or be less reliable. This problem is illustrated in ebola vaccine trials impacted by decline in cases. In an urgent pandemic situation, such loss of time is directly related to increased suffering. In some cases, this problem could be solved by using a controlled human infection model. Unfortunately, such models remain controversial in the case of a severe infection without adequate treatment, that has a widely varying severity in different risk groups. Additionally, these models are currently not regulatory acceptable as a surrogate for field trials. We therefore attempted to explore if the use of a “naturalistic infection model,” provided by an area with a rapidly increasing infection rate, such as local outbreaks or alternatively called “hot spot,” would shorten the time to determine vaccine efficacy and could consequently further expedite clinical development. Such local outbreaks could be identified on the level of communities, districts, cities, or even states/provinces. Because the study protocols and design for large-scale efficacy trials are largely standardized, we considered if there could be strategies used to shorten study duration by actively identifying and deploying trial activities deliberately in areas where an increase or resurgence of infections occurs, even after the study was started in another location. Such a dynamic approach may lead to faster identification of disease cases in both the active and placebo arms of the efficacy trial, as opposed to the traditional ‘wait-and-see’ approach. This novel strategy is clearly dependent on many factors and therefore ideally suited for trial simulation to study its feasibility. In this study, we performed a simulation of such a strategy. The model we developed is intended to have applications beyond the search for a covid-19 vaccine and should also be applicable for future pandemics and pandemic preparedness. To execute this strategy, dedicated mobile clinical trial teams should be formed and kept operational for a rapid response once an outbreak has been identified. We also supply suggestions for the needed equipment, composition and organization of such clinical trial teams that can quickly respond after the identification of an infection hot spot to further boost the feasibility of this strategy.

Methods

SIMULATION METHODOLOGY

The potential improvement of utilizing an active hot spot vaccination strategy was quantified in a clinical trial simulation performed in R V3.5.3. Details about the model selection, definitions, simulations and script can be found as Supplementary File. Infections over time were simulated and the commonly used ‘wait-and-see’ strategy was compared with the proposed active hot spot vaccination strategy. Table 1 shows the parameters used for the simulation of the infections over time in the general population and all parameters for the infections over time and identification criteria in a hot spot. A mean hot spot growth rate of 3% was chosen for the baseline scenario, resulting in a doubling of the number of infections after ~23-24 days. After a certain duration (40, 60, or 90 days) stringent government measures were put in place that immediately reduced the growth rate.

Furthermore, Table 1 provides information on logistics related characteristics, such as the maximal number of vaccinations per day that can be given and the percentage of the total vaccinations given in a hot spot. If a hot spot-based vaccination strategy was applied, the total number of vaccinations in the general population was set to $N_{\text{total}}-N_{\text{hot-spot}}$. Therefore, the total number of administered vaccinations (the total sample size) was identical in both strategies. In the scenario where no hot spot was simulated or could be identified, the $N_{\text{hot-spot}}$ vaccines were randomly distributed over the total population at day 100.

In order to explore the effect of both strategies on the study duration, the following simulation methodology was applied:
1. Simulate infection profile in the general population and in a hot spot, with a hot spot occurring after X days since start of study.
2. Run clinical trial simulation both on the wait-and-see and active hot spot vaccination strategy.
3. Randomly vaccinate subjects and randomly infect subjects, based on the daily infection rate for the general population and the hot spot.
4. Check each day if a hot spot was identified based on the hot spot identification criteria.
   a) If a hot spot was identified, start subject inclusions and additional vaccinations in the hot spot.
5. Count the cumulative number of infections after the time until vaccine effectiveness in the study population (both in the placebo and active group).
6. End the study if the target level of infections has been reached in the study population and record the total trial duration.

One each simulated infection profile, eight trial simulations were run (four per strategy), to account for the stochasticity in the random sampling procedure. Due to the variable nature and spread of (novel) pandemic infections, a local sensitivity analysis was performed to explore differences compared to the baseline scenario, in which one model parameter at a time was changed. For each scenario, 20 different infection profiles were simulated and analyzed to determine the mean and standard error of the study duration and the difference ($\Delta$) between the two strategies.

**Results**

*Figure 1* presents the baseline scenario of the number of infections over time in the general population and in a simulated hot spot. A clear increase in the number of infections can be observed in the hot spot with a corresponding reduction after stringent government measures were put in place. With the wait-and-see strategy, this hot spot population would only have received 5% (1000) of all vaccines in the study due to the random inclusion of subjects following this approach. The number of vaccinations in the hot spot is increased to 2900 (receiving an additional 10% of the vaccines) at seven days after the identification of a hot spot (three days before start vaccinations and four days of administering vaccines). By using the hot spot-based inclusion strategy the number of infections in the study population increased and thereby reduced the total study duration with 15 days in the baseline scenario, a 10% reduction of the study duration compared with the baseline scenario (*Table 2*).

*Table 2* and *Figure 2* show the differences between the wait-and-see versus active hot spot vaccination strategy for all the explored scenarios. These results show that in almost all the investigated scenario’s a reduction of the study duration was shown when applying the hot spot-based vaccination strategy. Especially when increasing the percentage of vaccines that were deployed in a hot spot up to 20%, which resulted in a 22.7 days decrease of the study duration. The only explored scenario in which an increase in duration was present was when no hot spot occurred and the withheld vaccines were administered as late as day 100, after which the study duration showed a minor increase from 157 to 162 days. These results indicate that regardless of potential changes in infections over time or lockdown measures in a hot spot (that would reduce the number of infections back to baseline) withholding part of the total vaccine pool for an active vaccination strategy has the potential to reduce the study duration with multiple weeks and only has a limited risk of increasing the study duration. Additionally, when lower baseline infection rates in the general population are present (leading to an increase in the study duration) and faster identification of the hot spot is possible (improving the benefit of the proposed strategy) an even larger reduction in study duration could be observed.

**RAPID RESPONSE TRIAL TEAM**

The lead time for the formation and operationalization of such a team should be as short as possible. Therefore, clinical trial teams should be kept in readiness and mobilized as soon as the phase I trials of new vaccines start in a pandemic. Teams should ideally be managed from a central location, for instance, from national public health organizations or the World Health Organization. Ideally such a strategy should be employed across different countries. An essential component of the strategy is the possibility to have approved standardized study protocols, where only pre-specified data of the vaccine must be inserted. Pandemic preparedness arrangements with pertaining authorities and ethics committees should exist for fast tracking the final approval with expected approval times of less than a week.
We recommend that rapid response trial teams are constituted on a national level but based upon international standards for training and equipment. If this is not feasible, trial teams should be deployed for low-to-middle wage countries or countries that lack sufficient clinical trial infrastructure or experience.

When a hot spot is targeted there will be little time for communicating and therefore generic communication plans for local and social media should be prepared in advance to improve local community engagement. Software systems will be an essential asset and should be set up for multilingual use and to require minimal or no paper administration (Table 3).

Discussion

Developing novel vaccines in a pandemic setting requires a different paradigm for clinical development. Our simulation demonstrates that a field trial can be expedited by adapting to the changing nature of disease incidence in a pandemic, but that this requires a speed of response that is unusual in the standard phase III clinical trial. The feasibility and success of performing large scale phase III field trials is dependent on the incidence of the disease in a population. If the incidence is relatively low this means that a large group of participants needs to be followed over a long time to encounter enough cases in the active/placebo arm of the trial. On the other hand, if the reproduction rate of the pathogen is too high, stringent government measures to reduce transmission within a population can hinder the feasibility to perform a field study and previously selected areas to study the vaccine might not have been optimal. When the preparation time for a trial is too long, the outbreak may already be under control in the place where the trial was intended. As a result, clinical trials are initiated in endemic countries with relatively high incidence of disease but may be prematurely halted due to dropping disease incidence. We suggest a strategy to expedite vaccine development where recruitment of participants is performed dynamically in areas where disease incidence rates are growing fast. By identifying local outbreaks and deploying mobile ground teams to move to these areas with high infection incidence, it is possible to conduct a clinical trial in a subgroup of volunteers with a high a priori risk of being exposed and infected to the pathogen. We demonstrate by our model that key endpoints such as disease incidence in these so called ‘hot spots’ can be reached more efficiently compared to the traditional wait-and-see approach.

The hot spot vaccination strategy described in this paper utilizes a more straightforward approach compared to other case-reactive vaccination strategy such as cluster or ring vaccination, used in ebola vaccine trials. The hot spot vaccination approach described in this paper simply aims to recruit, enroll and randomize subjects on an individual level, but dynamically in areas where there is a higher a priori risk of being exposed to the pathogen. Although a ring vaccination trial might be preferable in some outbreak situations, it has some inherent methodological drawbacks associated with cluster randomization.

The suggested hot spot approach has a few limitations that have to be noted. As with every clinical trial it is important to recruit and engage participants. Moreover, as the hot spot vaccination approach will be deployed in local outbreaks it is important to create local community engagement to participate in clinical research. Much of this will have to be done on a regular basis before a pandemic is identified and yearly pandemic
preparedness simulation exercises can be a good way to keep communities engaged. Our model had as the key outcome the proportional reduction of the incidence of disease. Other outcomes, such as reduction of infectivity or duration of protection do obviously require longer trials with more intensive sampling, but these outcomes could also be studied further after initial or conditional authorization of a vaccine to limit a pandemic. Last, as mentioned previously, the described strategy requires that sophisticated contact tracing for the pathogen is readily available.

For future pandemic preparedness, maintaining a mobile hot spot vaccination trial approach will require continuous financing for potentially long periods. Even if no local outbreak is identified, a study team needs to be on stand-by mode, ready to be deployed as soon as a hotspot is identified. The pharmacoeconomic evaluation of utilizing and maintaining this strategy falls beyond the scope of this paper. However, we feel that this investment is worthwhile given the merits of expediting the generation of efficacy data and accelerating vaccine development which ultimately has profound societal and economic impact. Such costs must be borne by funds from a dedicated pandemic defense budget, analogous to funding of military national defenses.

The applied simulation methodology was performed as a proof-of-concept, in which a combination of realistic baseline parameters for infection rates and hot spot parameters were applied. However, the performed local sensitivity analysis only shows the results of modifying one parameter at a time based on the baseline scenario. Changes in multiple parameters at the same time or scenarios with a completely different set of parameters are more likely depending on study logistics and infection characteristics. Clinical trial simulations in the future should therefore be adapted on a case-by-case basis. Furthermore, the current infection model treated the general population and the hot spot as independent populations in which growth rates were randomly sampled from uniform and normal distributions. The exponential growth rate in the hot spot switched to an exponential decline rate after a fixed number of days in this simulation. In reality, this switch would be more subtly caused by the stepwise introduction of governmental measures which would broaden the hot spot peak, and would further improve the benefit of a hot spot-based vaccination strategy. As this simulation was primarily focused on clinical trial design and execution, this model oversimplifies the complex epidemiological components of disease outbreaks and an extension with the modelling of mixing patterns could improve the precision of this simulation.

In conclusion, by investigating vaccine efficacy in clusters of subjects with a high risk of infection, efficacy data can be generated more efficiently, as is shown in our model. Our suggested hot spot-based vaccination approach may reduce clinical development time and thus, expedite clinical development of new prophylactic interventions in emergent pandemic situations and thus may save considerable opportunity costs and, above all, lives.
Chapter 7: Accelerating Vaccine Trials by Identifying Infection Hot-Spots — An In Silico Experiment

**Table 1** Baseline Parameters Used for the Simulation of Infection Rates Over Time, the Vaccine Effectiveness, and the Study Design (Logistical) Components in the General Population and in the Hot Spot.

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population pool size</td>
<td>10 million</td>
</tr>
<tr>
<td>Population size of general population</td>
<td>9.5 million (95% of total population)</td>
</tr>
<tr>
<td>Population size of hot spot</td>
<td>500,000 (5% of total population)</td>
</tr>
<tr>
<td>Minimal number of infections per day in population over time*</td>
<td>6 / 100,000</td>
</tr>
<tr>
<td>Day-to-day reproduction rate (not during hot spot)</td>
<td>-5% to 4.5% (uniform distribution, sampled at random per day)</td>
</tr>
<tr>
<td>Start of hot spot since start of trial</td>
<td>20 days</td>
</tr>
<tr>
<td>Daily growth rate in hot spot</td>
<td>Mean growth of 3% (normal distribution, standard deviation of 2%) per day</td>
</tr>
<tr>
<td>Duration of growth period</td>
<td>60 days</td>
</tr>
<tr>
<td>Daily decline rate after growth period until baseline is reached</td>
<td>-3%</td>
</tr>
<tr>
<td>Duration of lockdown period</td>
<td>40 days or until minimal number of infections was reached</td>
</tr>
<tr>
<td>Total number of vaccinations given and subjects included (N&lt;sub&gt;total&lt;/sub&gt;)</td>
<td>20,000</td>
</tr>
<tr>
<td>Number of random vaccinations given in total population per day</td>
<td>2,500</td>
</tr>
<tr>
<td>Time until effectiveness of vaccine (days)</td>
<td>21</td>
</tr>
<tr>
<td>Target total number of infections in study population for completion of study (% of study population)</td>
<td>100 (0.5%)</td>
</tr>
<tr>
<td>Effectiveness of vaccine</td>
<td>80%</td>
</tr>
<tr>
<td>Hot spot threshold value for identification</td>
<td>3 days of &gt; 1.5x the infection rate of general population (infections/100,000)</td>
</tr>
<tr>
<td>Time until start vaccination in hot spot after identification</td>
<td>3 days</td>
</tr>
<tr>
<td>Number of vaccinations given in hot spot population per day</td>
<td>500</td>
</tr>
<tr>
<td>Total number of vaccinations given in hot spot (N&lt;sub&gt;hot spot&lt;/sub&gt;)</td>
<td>2,000 (10% of total)</td>
</tr>
</tbody>
</table>

*Infections are constrained to not go below the baseline level of 6/100,000 to simulate an ongoing pandemic.
### Table 2: Difference in Trial Duration Using an Active Hot Spot Vaccination Strategy Compared to a Wait and See Approach.

Each row shows a component of the simulation that was altered and the resulting change between strategies. Δ hot spot vaccination strategy is the mean difference in study duration of 20 iterations for each scenario.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Value</th>
<th>Δ hot spot vaccination strategy (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline simulation</td>
<td></td>
<td>-15.36 (1.79)</td>
</tr>
<tr>
<td>Hot spot duration</td>
<td>40 days</td>
<td>-2.54 (2.09)</td>
</tr>
<tr>
<td>Hot spot duration</td>
<td>90 days</td>
<td>-17.29 (1.09)</td>
</tr>
<tr>
<td>Hot spot growth rate per day</td>
<td>2%</td>
<td>-3.64 (2.07)</td>
</tr>
<tr>
<td>Hot spot growth rate per day</td>
<td>5%</td>
<td>-2.7 (1.6)</td>
</tr>
<tr>
<td>Hot spot percentage of vaccinations</td>
<td>20%</td>
<td>-22.7 (2.04)</td>
</tr>
<tr>
<td>Hot spot percentage of vaccinations</td>
<td>5%</td>
<td>-5 (2.09)</td>
</tr>
<tr>
<td>Hot spot start vaccinations</td>
<td>5 days</td>
<td>-10.28 (1.9)</td>
</tr>
<tr>
<td>Hot spot start vaccinations</td>
<td>9 days</td>
<td>-13.29 (2.16)</td>
</tr>
<tr>
<td>Hot spot vaccinations per day</td>
<td>1000</td>
<td>-12.6 (1.65)</td>
</tr>
<tr>
<td>Hot spot vaccinations per day</td>
<td>2000</td>
<td>-13.9 (2.92)</td>
</tr>
<tr>
<td>Population size of hot spot</td>
<td>0.50%</td>
<td>-15.09 (2.16)</td>
</tr>
<tr>
<td>Population size of hot spot</td>
<td>1%</td>
<td>-13.85 (1.94)</td>
</tr>
<tr>
<td>Population size of hot spot</td>
<td>10%</td>
<td>-9.62 (1.79)</td>
</tr>
<tr>
<td>Onset of hot spot after start of study</td>
<td>60 days</td>
<td>-3.51 (1.6)</td>
</tr>
<tr>
<td>Onset of hot spot after start of study</td>
<td>Never</td>
<td>4.72 (2.15)</td>
</tr>
<tr>
<td>Time to vaccine effectiveness</td>
<td>14 days</td>
<td>-14.93 (2.21)</td>
</tr>
<tr>
<td>Time to vaccine effectiveness</td>
<td>28 days</td>
<td>-7.91 (1.91)</td>
</tr>
</tbody>
</table>

*Mean (standard error)

### Table 3: Practical and Personnel Requirements for Mobile Trial Units and Central Coordinating Center.

**Rapid Response Personnel**
- At central coordinating center:
  - Infectious disease specialist
  - Clinical epidemiologist/modeler
  - Logistic expert
  - Modeler/metrician
- In mobile units:
  - Technical staff (location management, security)
  - Pharmacy technicians
  - Nursing staff and trial physician

**Key Facilities Coordinating Center**
- Communication facilities to mobile center.
- Continuous access to epidemiological data.

**Other**
- Public (or access to) up-to-date data on disease incidence per region.
- Home-monitoring equipment and software.

**Key Facilities Hot Spot Site**
- Mobile vaccination center(s) (e.g., portacabin, repurposed existing community facilities).
- Transportable laboratory or infrastructure to centralize laboratory assessments.
- Mobile pharmacy and refrigeration units.

**IT Infrastructure**
- Mobile software applications for digital contact tracing.
- Dependent on location: csm and satellite communication equipment and internet connections.
- Reliable power supply.
- Digital infrastructure for informed consent procedure, recording of participant reported outcome measures and vital signs (home monitoring) and electronic case report forms.

**Communication Kits**
- Participants information text.
- Public media campaigns.
FIGURE 1  SIMULATED INFECTION PROFILES IN GENERAL POPULATION AND IN HOT SPOT OVER TIME (DAYS). The onset of the hot spot in the baseline scenario is 20 days since start study and continues up until 80 days since start study. Grey area shows 90% prediction interval of the baseline scenario. Black dashed lines show 20 random iterations of the baseline infection profiles.

FIGURE 2  MEAN OF THE STUDY DURATION FOR ALL EXPLORED SCENARIO’S AND BOTH STRATEGIES. ERROR BARS PRESENT THE STANDARD ERROR OF ALL ITERATIONS (N=20). The baseline scenario is included in each facetted labeled with the default parameter combination (e.g. hot spot duration of 60 days, hot spot size of 5%, etc.).
CHAPTER 8

HOW TO EXPEDITE EARLY-PHASE SARS-COV-2 VACCINE TRIALS IN PANDEMIC SETTING — A PRACTICAL PERSPECTIVE

Br J Clin Pharmacol 2021 May;87(5):2167-2169.
doi: 10.1111/bcp.14435

J.L van der Plas,1,2 M. Roestenberg,2,3 A.F. Cohen,1 I.M.C. de Visser-Kamerling,1 2,3

1. Centre for Human Drug Research, Leiden, nl
2. Department of Infectious Diseases, Leiden University Medical Center, Leiden, nl
3. Department of Parasitology, Leiden University Medical Center, Leiden, nl

SUPPLEMENTARY FIGURES AND TABLES

All mentioned supplementary figures and tables in this chapter can be found on the corresponding website by scanning this QR code.