Return to sport guidelines in athletes with selected acute respiratory infections, including COVID-19, based on clinical criteria and laboratory investigations

by

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DECLARATION

I, Carolette Snyders, the undersigned, declare that the dissertation and the research work contained therein, submitted to the University of Pretoria for the degree PhD in Sports Medicine, is my own original work and has not previously, either in its entirety or in part, been submitted to any other university.

Signed: 

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As my family is part of who I am, a personal word of gratitude to them in the ‘about the author’ section.

ABSTRACT

INTRODUCTION

An acute respiratory infection (ARinf) is the most common illness affecting athletes and can result in days lost to training/competing i.e. time loss, affecting safe return to sport (RTS). The RTS process is a continuum, consisting of two defined time points: days to return to training (RTT) and days to return to full performance (RTFP).

AIM

To formulate scientific and medically based RTS guidelines in athletes with recent ARinf, including COVID-19, based on clinical criteria and laboratory investigations. A secondary aim is to determine the incidence, and risk factors of ARinf, including SARS-CoV-2 in a cohort of athletes.

OBJECTIVES

To determine the incidence of SARS-CoV-2 in a cohort of athletes, explore factors associated with prolonged RTT, determine frequency of multi-organ involvement and determine factors associated with prolonged RTFP after SARS-CoV-2 infection in athletes.

METHODS

Study designs

Literature reviews: Systematic review with meta-analyses (ARinf) and narrative review (SARS-CoV-2). Original research: Cohort studies with retrospective (online questionnaire) and prospective (clinical assessment and follow-up) components.

Study setting

Sport, Exercise Medicine and Lifestyle Institute (SEMLI) clinical services, University of Pretoria, South Africa

Participants

Athletes with recent ARinf/SARS-CoV-2 infection

RESULTS

Main findings from the systematic review and meta-analysis were that 20% of suspected/confirmed ARinf result in time loss, with a mean symptom duration of 7 days. The narrative review highlighted the lack of scientific RTS guidelines after SARS-CoV-2 infection in athletes. Main findings from the original research were: 1) the incidence of ARinf (0.31) and SARS-CoV-2 (0.23) per 1000 player days was higher during contact vs. non-contact phases ($p<0.01$) and no factors were associated with the incidence of ARinf/SARS-CoV-2; 2) days to RTT and factors associated with prolonged (RTT) in athletes with recent SARS-CoV-2 infection were (univariate model): female ($p=0.01$), reduced training in the seven days pre-infection ($p=0.003$), presence of symptoms in "chest and neck" ($p=0.004$) and "whole body" ($p=0.025$) regions and multiple models showed greater number of symptoms in each anatomical region and total number of symptoms were significantly associated with prolonged RTT; 3) evidence of multi-organ involvement (10-28 days since onset of SARS-CoV-2) was found in 93-100% of athletes, consisting of residual symptoms (87%), abnormal clinical signs (46%) or abnormal laboratory investigations (60-75%), and total number of acute symptoms was a measure of disease severity, with >5 symptoms associated with higher risk for multi-organ involvement; and 4) days to RTFP (median;IQR) in symptomatic athletes was twice as long (64;42-91) than in asymptomatic athletes (30;23-40) ($p=0.026$). Factors associated with prolonged RTFP (univariate model) were: females ($p=0.014$), endurance athletes ($p<0.0001$), number of co-morbidities ($p=0.001$) and history of respiratory disease ($p=0.026$), and in multiple models, an increase in the number of total symptoms and symptoms in each anatomical region, remained significantly associated with RTFP.

CONCLUSION

Symptoms (type and number) during the acute phase of SARS-CoV-2 infection, may indicate severity of infection (multiple organ involvement), and predict duration for RTT and RTFP - thus forming the basis of practical and scientific RTS guidelines. Future research should determine if acute phase symptoms are associated with RTS outcomes in other ARinf.

KEYWORDS

Respiratory infection, COVID-19, SARS-CoV-2, athlete, return to sport, symptoms, recovery, assessment, predictors, investigations

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LIST OF ABBREVATIONS

ACSM	American College of Sports Medicine
ALT	Alanine transaminases
ARill	Acute respiratory illness
ARinf	Acute respiratory infection
AST	Aspartate transaminases
AWARE	**A**thletes **W**ith **A**cute **R**espiratory Inf**E**ctions
BMI	Body mass index
C	Competition
CI	Confidence interval
CK	Creatine kinase
CMR	Magnetic resonance imaging
CPET	Cardiopulmonary exercise test
CRP	C-reactive protein
CT	Contact training
CXR	Chest X-ray
Diff	Differential
ECG	Electrocardiogram
ECHO	Echocardiogram
FBC	Full blood count
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GIT	Gastrointestinal tract
HR	Heart rate/Hazard ratio

hs-cTnT	High sensitivity cardiac Troponin T
IOC	International Olympic Committee
IQR	Interquartile range
IR	Incidence ratio
ISEM	Institute of Sport and Exercise Medicine
IT	Individual training
LGE	Late gadolinium enhancement
LLN	Lower limit of normal
LRTI	Lower respiratory tract infections
LVEF	Left ventricular ejection fraction
mmHg	Millimetre of mercury
NCT	Non-contact training
Nr Inf	Number of infections
PCR	Polymerase chain reaction
PFT	Pulmonary function test
PPE	Pre-participation evaluation
PPI	Patient and public involvement
Q1	Quartile 1
Q3	Quartile 3
REDCap	Research Electronic Data Capture
RTFP	Return to full performance
RTS	Return to sport
RTT	Return to training
SAMRC	South African Medical Research Council

SD	Standard deviation
SEM	Sport and Exercise Medicine physician
SEMLI	Sport, Exercise Medicine and Lifestyle Institute
Trop T	Troponin T
URT	Upper respiratory tract
URTI	Upper respiratory tract infection
WCC	White cell count
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Acute respiratory infections in athletes

Acute respiratory tract infection (ARinf) is the most common acute illness affecting people of all ages worldwide[1] and is a major cause for morbidity and mortality.[2] Athletes are generally considered healthy individuals with exceptional physical capabilities as they challenge the body's limitations during training and sport participation. However, athletes are not exempt from acute illness, especially ARinf. Epidemiological studies (conducted before the COVID-19 pandemic), indicated the incidence of acute illness in athletes during 2-6 week tournaments ranged from 5-12%.[3-7] In all these studies, approximately 50% of these resulted from suspected or confirmed ARinf, making it the most common acute illness in athletes.

There are many risk factors associated with suspected or confirmed ARinf among athletes. These factors have recently been reviewed in a systematic review.[8] Risk factors and biomarkers with 'good' or 'strong' association with ARinf included: 1) type of sport (endurance sport[9]), 2) training/competition factors (intense training load,[10 11] increased strength and speed training,[11] endurance preparation phase[12] as well as competition period[13]), 3) environmental/exposure factors (winter,[11 12] training at high attitude > 1500 metres above sea level,[12] longer international travelling[12 14]), 4) nutritional factors (reduced serum vitamin D levels[15 16]), and 5) immune/haematological risks (decline in salivary IgA).[16] There is some evidence that female athletes have a higher risk for acute illness than their male counterparts[7 17 18] and lifestyle choices such as smoking can increase susceptibility to ARinf.[19] It was also documented that psychological stress[20] and allergies[21] can predispose an athlete to acute illness.

SARS-CoV-2 infection in athletes

Recently, the emergence of the COVID-19 pandemic, caused by the novel coronavirus (SARS-CoV-2), added a significant health burden on athletes and impacted sport participation globally. Access to training facilities were denied or restricted and many regional, national and international sporting events were cancelled. As restrictions were gradually lifted and sport was resumed, risk factors associated with transmission during sport

were unknown. Data on the incidence of SARS-CoV-2 infection and factors associated with this infection in the athletic population, were limited.

In addition, potential health consequences of athletes returning to sport after SARS-CoV-2 infection were largely unknown. Sport participation during, or soon after an ARinf (including SARS-CoV-2 infection), can potentially pose a risk of serious medical complications because of multi-organ dysfunction in the exercising athlete. Examples of specific organ involvement caused by ARinf pathogens (including SARS-CoV-2) resulting in medical complications include: lung involvement presenting as pneumonia,[22-25] or bronchitis,[23 26 27] cardiac involvement presenting as myocarditis,[24 28-30] pericarditis[31] or arrhythmias,[32] liver involvement presenting as hepatitis,[24 26] gastrointestinal tract involvement presenting as abdominal pain, nausea and vomiting,[33 34] and brain or meningeal involvement as meningitis[22 23] or encephalitis.[22 23] In addition to all the above mentioned possible organ involvement, SARS-CoV-2 infection can also present with unique clinical manifestations, including altered sense/loss of smell[35] and taste,[36 37] dermatological manifestations[38] and other neurological symptoms[39 40] or prolonged sequel, termed "Long-COVID".[41-43]

The literature available on clinical presentation and organ involvement of SARS-CoV-2 in athletes, grew substantially from 2020 to date. However, the main focus was on the cardiovascular system,[30 44-48] with few original research on other organ involvement. Organ system involvement as a result of SARS-CoV-2 infection can be defined as any residual symptom, abnormal clinical finding or abnormality on laboratory investigations in an organ system. Knowledge of multi-organ involvement can provide insight in possible organ dysfunction that may affect the response to exercise. This is important for clinical decision-making by the sport and exercise medicine (SEM) physician to guide the athlete in returning to full sports participation. Factors that are associated with a higher risk of multi-organ involvement in athletes with recent SARS-CoV-2 infection need to be determined, as these may prompt the physician to perform additional investigations and assist in determining the severity of the recent illness. Evidence of multi-organ involvement may result in prolonged return to training and require closer monitoring as training load increases and athletes adapt to training. More research in this field is important to safely guide athletes back to training and full performance.

Return to sport guidelines after acute respiratory infection (including SARS-CoV-2) in athletes

An athlete with an acute respiratory infection may have to abstain from exercise training, thus losing time from training or competition. This "time loss" has been defined in an "*International Olympic Committee (IOC) consensus statement on the epidemiological reporting of illness and injury in athletes*", as the number of days from the onset of symptoms to the day an athlete is fully available for training/competition, thus return to sport. This time loss also serves as a measure of illness/injury severity.[49]

In the field of Sport and Exercise Medicine, the term "return to sport" (RTS) is well established. The majority of the scientific literature on RTS protocols is focused on injured athletes.[50-54] Although RTS guidelines for athletes with a recent acute illness, specifically acute infection have been described[55] there is little scientific evidence to support these guidelines.

The current clinical guidelines for RTS after an acute respiratory infection are known as the "neck check", and were first proposed by a clinician in 1983.[55] These clinical guidelines separate illness symptoms into two categories, above the neck (nasal congestion, sore throat etc.) and below the neck (fever, severe cough, malaise and/or gastrointestinal symptoms). If symptoms are present above the neck, the athlete is allowed to train at 50% of normal training intensity for 10 min. If symptoms do not worsen during exercise, the exercise session can continue as tolerated. If symptoms are aggravated, exercise should be discontinued until symptoms improved. To our knowledge, these guidelines have never been systematically studied.

In recent years, in response to the COVID-19 pandemic, several guidelines to resume training after a SARS-CoV-2 infection have been published. In the initial months after the start of the COVID-19 pandemic, these guidelines were proposed by multiple expert opinions,[46 56-59] but the scientific basis to support these guidelines was limited because no original data were available.

After an ARinf, the athlete and coach are concerned about the timelines (days) to return to training and ultimately reaching pre-infection level of sports performance, while the SEM physician is challenged with providing medical clearance and assist with safe guidelines along these timelines.

A fairly recent and important concept is that RTS is a process, and not a single time point.[60] The term RTS is best used to describe the process of clinical decision-making on a continuum to determine when an athlete can return safely to full sports participation following an injury or illness.

The initially proposed continuum for RTS after injury[60] can be adapted for acute illness, and consists of two key decision making time points. The first decision the SEM physician needs to make, is when an athlete can go back to the first training session, and this can be defined as return to training (RTT). This will also include recommended medical screening tests before exercise training can resume, if clinically indicated. Once RTT commences, training load can progressively increase and finally, the second decision can be made when an athlete can return to competition or train at the pre-infection level of sports performance (return to full performance - RTFP). The time course (days) to RTT and RTFP after ARinf in athletes, as well as factors associated with the RTT and RTFP time points, are not well established. This information will assist the athlete, coaching staff and medical professional in planning safe RTS for the athlete.

1.2 RESEARCH PROBLEM STATEMENTS IN THIS THESIS

In summary, the following research problems and knowledge gaps were identified as the focus for this thesis:

1. ARinf is the most common cause of illness in athletes. Recently SARS-CoV-2 added to this health burden, however the incidence of SARS-CoV-2 and associated risk factors are not well documented in the athletic population.
2. The SEM physician is responsible to minimise potential medical risks during respiratory infections in the exercising athlete. There is evidence in the general population that ARinf, including SARS-CoV-2 infection can affect multiple organs.[61] Knowledge on how multiple organ systems can potentially be affected is necessary to provide safe return to sport guidance. Currently, data on multi-organ involvement by SARS-CoV-2 infection in athletes are limited to the cardiovascular and respiratory systems. It is not known how common multi-organ involvement is in athletes with SARS-CoV-2 infection, and what potential factors are associated with higher risk of multi-organ involvement.

3. Returning to sport after ARinf is a process not a single time point. RTS is characterised by clinical decisions related to when an athlete can return to training (RTT), and when the athlete can return to full performance (RTFP). The days to RTT and RTFP in athletes with recent history of ARinf, including SARS-CoV-2 infection, has not been well described, and factors affecting days to RTT and RTFP have not been investigated.

1.3 STUDY AIM AND OBJECTIVES

The aim of this thesis is to formulate scientific and medically based return to sport guidelines in competitive athletes with selected acute respiratory infections (ARinf), including COVID-19, based on clinical criteria and laboratory investigations. A secondary aim is to determine the incidence, and selected risk factors of ARinf (including COVID-19) in competitive athletes. There are four distinct objectives in this thesis:

Objective 1

To determine the incidence (per 1000 player days) of ARinf in student rugby players during different phases of return to competitive sport following lockdown during the COVID-19 pandemic. Additionally, acute phase symptoms and factors associated with ARinf, will be explored.

Objective 2

To determine factors associated with prolonged return to training (RTT) in athletes with recent SARS-CoV-2 infection

Objective 3

To determine the frequency (%) of multi-organ involvement and explore if greater number of symptoms during the acute SARS-CoV-2 infection phase was associated with demographics, sport type, history of co-morbidities and multi-organ involvement.

Objective 4

To identify factors associated with a prolonged time course (days) to return to full performance (RTFP) in a cohort of athletes with a recent SARS-CoV-2 infection.

1.4 CONCEPTUAL FRAMEWORK

In this thesis, the literature on return to sport guidelines, both by expert opinion and available research studies, will be reviewed to identify knowledge gaps where further research is needed. The review process consists of a systematic review and meta-analysis, followed by an updated narrative review of studies during the COVID-19 pandemic. The aim of the studies presented in this thesis is to fill some of these existing knowledge gaps identified by the reviews of return to sport after acute respiratory infection. A series of original research studies were conducted to answer key objectives. Finally, the results of the studies will be summarised in RTS guidelines after ARinf, based on clinical criteria and laboratory investigations. The conceptual framework of the thesis is outlined in Figure 1.

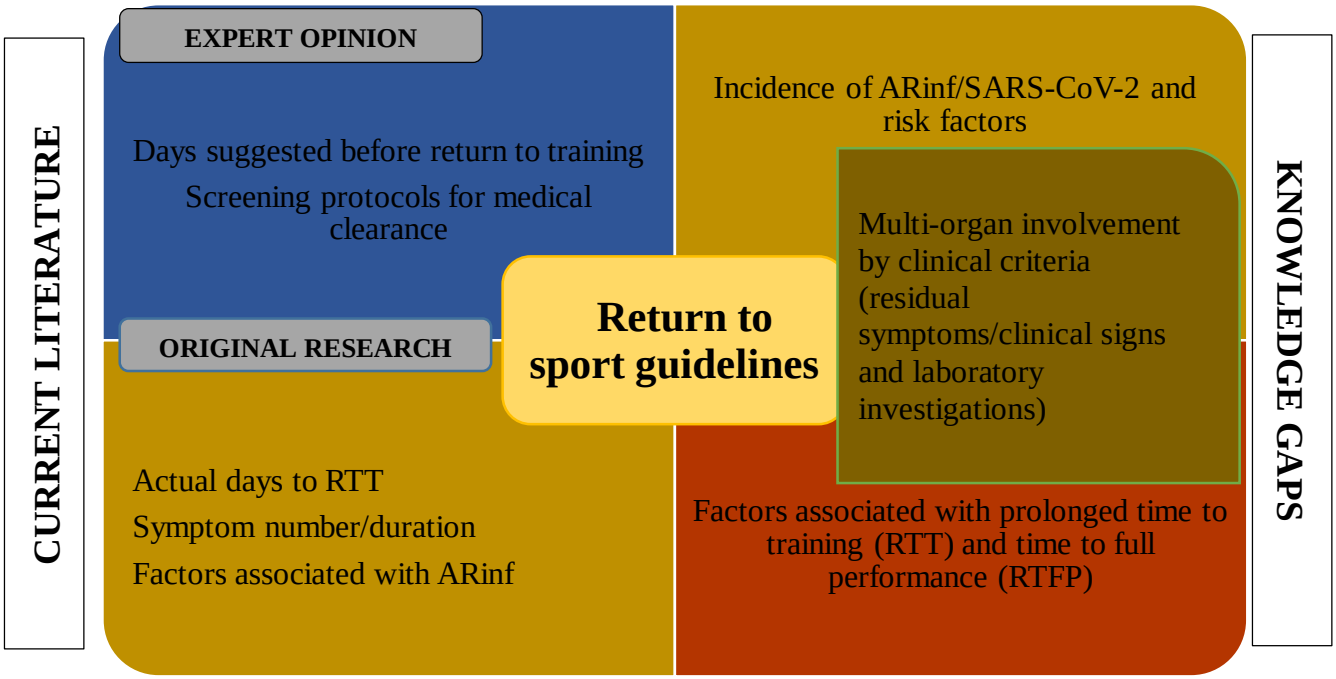

Figure 1: Conceptual framework of the thesis

1.5 GENERAL METHODS OF STUDIES IN THIS THESIS

Study designs and settings

Study designs

The first study in this thesis was a systemic review and meta-analysis, which followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[62] guidelines. The study was registered with the international prospective register of systematic reviews (PROSPERO) number CRD42020160479. The full detailed methods are described in the chapter where this study is reported. There are four original research studies consisting of study designs as follows: 1) a retrospective cohort study design, which is used for objectives 1 and 2, and 2) a prospective cohort study with cross-sectional analyses, which is used for objectives 3 and 4. The full detailed methods used in each of these studies, are described in the relevant chapters.

Study settings

The retrospective studies were conducted by means of an online survey instrument (questionnaire) and were part of a study with national and international collaborators. The prospective cohort study was conducted at the clinical service facilities of the Sport, Exercise Medicine and Lifestyle Institute (SEMLI) at the University of Pretoria, South Africa. The detailed methods are discussed in the each of the subsequent chapters.

Study protocols and ethical considerations

Prior to commencing with the research described in this thesis, the PhD study protocol was approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria, South Africa (Title: "Return to sport guidelines in athletes with selected acute respiratory infections, including COVID-19, based on clinical criteria and laboratory investigations" - REC 751/2019).

This research study included components of several "umbrella" research studies that were also approved by the Research Ethics Committee of the Faculty of Health Sciences of the University of Pretoria, South Africa. These included the following:

1. "Athlete With Acute Respiratory InfEction (AWARE) Study: Part I" (REC number: 409/2020), and

2. "Athlete With Acute Respiratory InfEction (AWARE) Study: Part II- Prospective cohort with repeated experimental measures" (REC number: 644/2020)

1.6 THESIS OUTLINE

This thesis consists of the following 8 chapters:

Chapter 1

This chapter is a broad introduction to the thesis. It provides an overview of the problem statement, knowledge gaps, aims and objectives of the thesis, a general overview of the methods used in the thesis, and summarises the chapters presented in the thesis.

Chapter 2

Chapter 2 is a systematic review and meta-analysis titled: "*Acute respiratory illness and return to sport: A systematic review and meta-analysis by a subgroup of the IOC consensus on "Acute respiratory illness in the athlete*". The PhD fellow was the principal author of this review. This review was commissioned and conducted by a sub-group of an IOC Consensus group on "Acute respiratory illness in the athlete", that was chaired by the principal supervisor of this PhD thesis. This review was commissioned and commenced before the COVID-19 pandemic and was completed in 2020, during the pandemic. The focus was to review the days until return to sport (RTS) after acute respiratory illness (ARill), frequency of time loss after ARill resulting in >1 day lost from training/competition, and symptom duration (days) of ARill in athletes. This study has been published in the '*British Journal of Sports Medicine*' (BJSM).[63]

Chapter 3

Chapter 3, titled "*Acute SARS-CoV-2 infection and return to sport in athletes: A narrative review",* is part of the literature review component of this thesis. The aim of this review was to update and complement the systematic review presented in Chapter 2, with the specific focus on SARS-CoV-2 in athletes. As mentioned, the systematic review commenced before the onset of the COVID-19 pandemic and was completed in 2020, during the early phases of the pandemic. Therefore, the systematic review (Chapter 2) does not include any data on RTS following COVID-19, because the first original research on this topic was only published in

February 2021. Therefore, the literature in Chapter 3 includes data that were reviewed on a continuous basis throughout the PhD study as data became available on new insights and research questions that evolved during the COVID-19 pandemic. This dynamic process of literature review and analysis of published scientific studies, form the basis of the updated review, presented in Chapter 3. The review follows a chronological order of information that became available during the COVID-19 pandemic. Specifically, the following data were included: recommended days of rest before training should resume (by expert opinion) and screening protocols, both before and after original research became available, as well as actual days (from original research studies) since diagnosis or onset of symptoms of SARS-CoV-2 infection to RTT. Additionally, it reviewed symptom duration and symptom number during the acute phase of infection, as well as factors associated with RTT. Therefore, this chapter represents available data on RTS after SARS-CoV-2 infection in athletes up to October 2022.

Chapter 4

The first research study presented in this thesis (Chapter 4) is an original research study titled *"Incidence of respiratory infections (including SARS-CoV-2) is higher during contact training and competition compared to non-contact phases in a cohort of student rugby players – AWARE V".* This study investigated the incidence of ARinf (including SARS-CoV-2) per 1000 player days in a cohort of student rugby players (objective 1). This first study was part of the original PhD proposal to define the extent of the problem, and to identify risk factors associated with the presenting problem – the first step in the Van Mechelen model of epidemiological research on injury (and illness).[64] In the original proposal, this was designed to explore different pathogens, but had to be modified to focus only on SARS-CoV-2 infection, because of the unique circumstances around the time of the pandemic. In keeping with the original objective, factors associated with incidence of SARS-CoV-2 infection in athletes in this cohort were also explored. A detailed literature search on the epidemiology of non-SARS-CoV-2 infections in athletes is not included in this thesis. However, a literature review on the epidemiology of SARS-CoV-2 infection in athletes was performed, and is included in the introduction section of this original research paper. This study has been submitted for publication in the journal '*Sports Health*' and is currently under review. Comprehensive systematic reviews on the epidemiology[65] and risk factors associated with ARinf in athletes[8] were recently published.

Chapter 5

Chapter 5 is an original research study titled *"Symptom number and reduced pre-infection training predict prolonged return to training after SARS-CoV-2 in athletes: AWARE IV".* The aim of this study was to determine factors associated with prolonged return to training (RTT) in athletes with recent SARS-CoV-2 infection (objective 2). The following factors were explored: demographics (age and sex), sport participation (level and type of sport), history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits (smoking and alcohol consumption). This study was published in the journal '*Medicine & Science in Sports & Exercise*' (MSSE).[66]

Chapter 6

Chapter 6 is an original research study titled *"Number of acute symptoms is associated with multi-organ involvement in athletes with recent SARS-CoV-2 infection: AWARE VII".*
In this study, the frequency (%) of multi-organ involvement defined as residual symptoms, abnormal clinical signs or laboratory investigations among athletes presenting 10-28 days after acute SARS-CoV-2 infection (objective 3), was determined. It also investigated if greater number of symptoms during the acute SARS-CoV-2 infection phase was associated with demographics, sport type, history of co-morbidities and multi-organ involvement (objective 3). This study has been submitted to '*Medicine & Science in Sports & Exercise*' (MSSE).

Chapter 7

Chapter 7 is an original research study titled *"Increased number of symptoms during the acute phase of SARS-CoV-2 infection in athletes is associated with prolonged time to return to full sports performance – AWARE VIII".* The aim of the study was to determine if factors are associated with a prolonged time course (days) to return to full performance (RTFP) in a cohort of athletes with a recent SARS-CoV-2 infection (objective 4). This study has been submitted to '*British Journal of Sport Medicine*'.

Chapter 8

Chapter 8 focuses on a summary and conclusion of all the relevant findings of this PhD thesis in order to provide scientific and clinically-centred return to sport guidelines to athletes with a recent ARinf. Limitations of the recent studies and suggestions for future research are also discussed.

The study objectives are explored in different chapters as depicted in Figure 2.

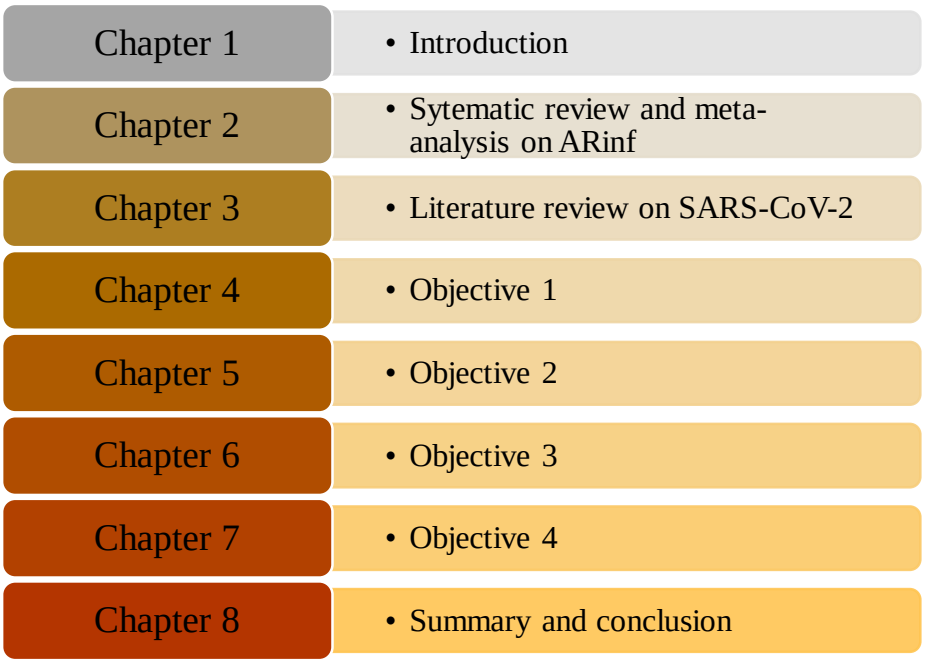

Figure 2: Objectives addressed in this thesis by chapters
ARinf, acute respiratory tract infection

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CHAPTER 2

Acute respiratory illness and return to sport: A systematic review and meta-analysis by an IOC consensus subgroup on "Acute respiratory illness in the athlete"

2.1 ABSTRACT

Objective

To determine the days until return to sport (RTS) after acute respiratory illness (ARill), % time loss ARill (ARill resulting in >1day lost from training/competition), and symptom duration (days) of ARill in athletes.

Design

Systematic review and meta-analysis

Data sources

PubMed, EBSCOhost, Web of Science, January 1990-July 2020

Eligibility criteria

Original research articles published in English on athletes/military recruits (15-65 years) with symptoms/diagnosis of an ARill, study that reported any of the following: days until RTS after ARill, frequency (%) of time loss ARill (i.e. loss of >1day) or symptoms duration (days) of ARill.

Results

767 articles were identified; 54 were included (n=31065 athletes). 4 studies reported days until RTS (range: 0-8.5 days). Frequency (%) (95%CI) of time loss ARill was 20.4% (15.3–25.4). The mean symptom duration for all ARill was 7.1 days (6.2–8.0). Results were similar between subgroups: pathological classification (acute respiratory infection [ARinf] vs. undiagnosed ARill), anatomical classification (upper vs. general ARill), or diagnostic method of ARinf (symptoms, physical examination, or special investigations identifying pathogens).

Conclusions

In 80% of ARill in athletes, no days are lost from training/competition. The mean duration of symptoms of ARill in athletes was 7 days. Outcomes were not influenced by pathological or anatomical classification of ARill, or in ARinf diagnosed by various methods. Current data are limited, and future studies with standardised approaches to definitions, methods of diagnosis and classifications of ARill are needed to obtain detailed clinical, laboratory and specific pathogen data to customise RTS.

PROSPERO registration number CRD42020160479

2.2 INTRODUCTION

The International Olympic Committee (IOC) is committed to protecting the health of the athlete.[1] Acute illness threatens athlete health and wellbeing, and can lead to interruption of training, withdrawal from competition and financial loss for professional athletes.[2 3] An acute illness causing delayed time to return to sport (training and/or competition) is referred to as a "time loss" illness.[4]

In athletes, the respiratory tract accounts for ~50% of all acute illness episodes,[5-9] and the majority of acute respiratory illnesses (ARill) in athletes are acute respiratory infections (ARinf).[6-10] The annual incidence of ARinf in the general adult population is about 2-3 episodes per year.[11] Physically active individuals typically have a lower incidence of ARinf compared with sedentary individuals, but competitive athletes may be more susceptible to ARinf, especially during periods of intense training and competition (J-shaped curve).[12] Elite athletes accustomed to very high training and competition loads may be less prone to ARinf (S-shaped curve).[13-15]

The sport and exercise medicine (SEM) physician is responsible for guiding the athlete with recent ARill to full and safe sports participation in the shortest possible time, while minimising the risk of potential medical complications. Evidence-based clinical guidelines to assist the SEM physician to decide on return to sport (RTS) after ARinf are lacking. RTS can be defined as "the time (days after the onset of an injury or illness), when the ill or injured athlete can return to pre-illness/injury level of activity and full training and competitive sports activities, with no limitation in performance or additional risk of medical complications".[16 17]

Symptoms of an acute illness are widely used in RTS decision making, specifically for ARinf.[18-20] Historically, athletes with localised symptoms of ARinf above the neck (e.g. sore throat, rhinorrhoea or nasal congestion) were advised that exercise can resume at a low intensity for a short duration, and if exercise is well tolerated, training can continue. If symptoms are below the neck (e.g. fever, myalgia or cough), the athlete was advised to rest until symptoms have resolved. These guidelines are referred to as the 'neck check'.[19] There is no scientific evidence for these guidelines and the validity of the 'neck check' as a guide for RTS has been challenged.[21] Despite the lack of data, the presence and nature (type) of regional/systemic symptoms is still a key component of most clinical decision-making guidelines for RTS following ARinf in athletes.[22-24]

Several studies report the frequency (%) of ARill that result in interruption from training/competition for >1 day (% of time loss ARill), while other studies report the duration of symptoms (days) of ARill. The frequency (%) of time loss ARill is defined as the number of ARill that resulted in time loss >1 day from training or competition (numerator) divided by all the ARill (denominator), expressed as a %. Few studies report the actual days until RTS following ARill in athletes. Data from all these studies have not been reviewed systematically.

A systematic review with a meta-analysis was undertaken to determine the effects of ARill on RTS in athletes. Specific outcomes were days to return to sport (RTS), frequency (%) of time loss ARill (ARill resulting in interruption of training/competition >1 day), and the mean duration of symptoms (days) of ARill. We also sought to determine outcomes in subgroups of ARill in athletes, based on the method used for the diagnosis of ARill, pathology (ARinf vs. undiagnosed ARill), and predominant anatomical region affected [upper vs. lower respiratory tract or general (upper/lower)]. The impact of ARill on other training/competition variables was also explored.

2.3 METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[25] guidelines were used.

Study selection and eligibility criteria

Articles that fulfilled the following criteria were included:

1. Male or female participants (15–65 years), athletes at any level (recreational to elite), or military recruits engaged in training
2. Participants with a diagnosis of ARinf (suspected or confirmed) or a mixed ARill (infective and non-infective)
3. Studies reporting any of the following variables: days lost to training/competition or return to sport following an ARill, % ARill's in athletes resulting in time loss >1 day lost from training or competition (time loss ARill), the duration of symptoms of ARill or the time to recovery from ARill (days)
4. Original research journal articles
5. Full-text articles published in English between 1 January 1990 and 31 July 2020

Articles in non-human studies, those that reported chronic respiratory illness (including malignancy) or only non-infective ARill (e.g. allergic rhinitis or asthma), review articles, expert opinions, position statements, single case-studies, conference abstracts, book chapters, and commentaries were excluded.

Search strategy

PubMed, EBSCOhost and Web of Science (Core Collection) databases were searched for articles. Search terms were combined in 3 search strings of key terms relating to (1) acute respiratory illness, (2) athletes/active individuals, and (3) return to sport, joined with 'AND'. The terms within the strings were joined by 'OR', and those not deemed relevant to the study question were excluded by using 'NOT' (online supplementary file 1). Search results were combined, and duplicate articles removed. Article screening and selection was conducted with the online tool CADIMA (version 2.2.1).[26] Two independent reviewers (CS, DP) screened all articles, first by title and abstract, and then by full text. References and reviews were searched manually to identify additional articles. Disagreement among reviewers were resolved by consensus. The final selection of articles was cross-checked by two additional reviewers (MS, NS).

Data Extraction

We used the term 'athletes' to combine diverse levels of sports participation and included military recruits (trainees regarded as active individuals). Participant demographics and

details of data extracted for analyses from each article are summarised in online supplementary tables A and B respectively. The following data were extracted: participants (number, age, sex), study design, type of sport or sporting event/military, level of participation (recreational/amateur/military or elite/professional/international/national), length of study surveillance, method used for the diagnosis of ARill and classification of ARill (pathological/anatomical classification), number days lost (>1) from training/competition due to ARill, duration of ARill symptoms, and the possible impact of ARill on training/competition variables. In randomised control studies, only results from control group were extracted.

Definitions and classification of subgroups of ARill

Pathological classification

Methods to diagnose an ARill, and specifically an ARinf vary substantially and include typically symptoms, findings on clinical examination, and/or special investigations to identify a specific pathogen. We developed a classification system to categorise the methods to diagnose ARill in each study as follows: (1) self-reported symptoms of ARill only, (2) self-reported symptoms combined with an algorithm at least partially validated for ARinf, (3) self-reported symptoms of an ARinf reviewed by a physician, but without clinical or laboratory evaluation, (4) clinical diagnosis of an ARinf by a physician, based on history and clinical examination, and (5) clinical diagnosis of ARinf by a physician confirmed by laboratory investigation to identify a specific pathogen(s) as follows: polymerase chain reaction (PCR) testing on specimen(s), culture of an organism(s) from specimen(s), or serology (e.g. rise in antibody titres). Data were extracted for each study and agreed by consensus (CS, DP, NS, MS). Once studies were classified by the five methods of diagnosis, all ARill studies were included in one of the following main and subgroups of ARill, based on a pathological classification (Table 1).

Table 1: Pathological classification (main and subgroups) of acute respiratory illness (ARill) by diagnostic method

Pathological classification		Methods to diagnose ARill	Description
Main group	**Subgroup**		
Undiagnosed ARill		• Self-reported symptoms of ARill only • Self-reported symptoms combined with an algorithm at least partially validated for ARill • Self-reported symptoms of an ARill reviewed by a physician, but without clinical or laboratory evaluation • Clinical diagnosis of an ARill by a physician, based on history and clinical examination	• General symptoms of an ARill where the pathology could not be attributed specifically to an infection • ARill studies could include illnesses that are due to either infective or non-infective causes but were not specified in the study design
ARinf	Suspected acute respiratory tract infection (ARinf)	• Self-reported symptoms combined with an algorithm at least partially validated for ARinf • Self-reported symptoms of an ARinf reviewed by a physician, but without clinical or laboratory evaluation • Clinical diagnosis of an ARinf by a physician, based on history and clinical examination	• General symptoms and/or physical signs suggestive of an ARinf, but where the pathology of an infection was not confirmed • The validated questionnaires that were used including the Wisconsin Upper Respiratory Symptom Survey (WURSS-21®)[27], the Jackson Cold Scale (JCS)[28], or other questionnaires in which the severity of the symptoms were scored to provide a quantitative assessment,[29 30]
	Confirmed acute respiratory tract infection (ARinf)	• Clinical diagnosis of ARinf by a physician and confirmed by laboratory investigation to identify a specific pathogen as follows: polymerase chain	• In some cases, a diagnosis of an ARinf caused by a specific pathogen can also be regarded as confirmed when diagnostic clinical features with a high sensitivity and specificity

		reaction (PCR) testing on specimen(s), culture of an organism from specimen(s), or serology (e.g. rise in antibody titres)	are present in suspected cases • In such case there is also a high pre-test probability • of an ARinf (e.g. a history and typical rash in an athlete where there is a confirmed viral outbreak in a travelling team, or during an epidemic/pandemic)

ARinf, acute respiratory infections

Anatomical classification

ARill (including ARinf) frequently present with both upper and lower respiratory tract symptoms/signs, and it is not always possible to clearly distinguish between these main anatomical regions when classifying ARill. A limitation of this anatomical classification is that several pathogens that cause predominantly upper ARinf can, in some cases, present with lower respiratory and/or systemic symptoms. In most studies of ARill in athletes, there is a clear distinction between upper and lower ARill, and upper ARinf (suspected or confirmed) is the most common acute illness in athletes.[6-10] Thus, from a clinical/pragmatic point of view we deemed it relevant to include an anatomical classification of ARill in the review. We classified studies into the following subgroups, based on the predominant anatomical region affected:

- Upper (ARill or ARinf): Studies where the predominant symptoms, signs, or confirmed pathology was mainly related to the upper respiratory tract (i.e. above the larynx), or if the study specifically referred to athletes with upper ARill or ARinf. A few studies referred to ARinf with non-specific terms such as “flu”, “flu symptoms”, “common cold”, “symptoms suggestive of influenza”, “influenza symptoms” or “influenza like”. Studies referring to these clinical syndromes were also included in this broad anatomical classification because they are caused by pathogens that all present with predominantly upper respiratory tract symptoms.[31-34] Notably, this includes the influenza viruses, which predominantly present with upper respiratory tract symptoms[35] and are listed as a cause of upper respiratory tract infections.[31 32 33]
- *Lower (ARill or ARinf)*: Studies where the predominant symptoms or signs were below the larynx (including chest symptoms i.e. cough, chest pain), or if a confirmed diagnosis

specifically referred to athletes with mainly lower respiratory illness (tracheal, bronchial or lung pathology e.g. pneumonia).

- *General (upper/lower) (ARill or ARinf)*: Studies where there were no data to clearly distinguish between predominantly upper/lower respiratory ARill. These studies could include upper, lower or both.

Quality Assessment and risk of bias

The Downs and Black tool[36] was modified by removing questions pertaining to randomised controlled trials as this review only included studies using participants and outcomes (PO). A score out of 13 (online supplementary file 2) was used to determine the quality of articles. The tool consisted of items as follow: reporting, external validity, internal validity (bias and selection bias). Each item was scored as 'yes' (score=1), 'no' (score=0) or 'undetermined' (score =0). Two reviewers (CS, DP) independently scored articles, and after discussions agreed on the final score for each article by consensus (online supplementary table C). The level of evidence was determined using the Oxford Centre for Evidence Based Medicine (OCEBM, 2009).[37] (online supplementary table C)

Outcome Measures

There were four outcome measures as follows:

Days until return to sport (RTS) after an ARill

The number of days to RTS after an ARill was taken as the reported days lost in training/competition due to the ARill.

Frequency (%) of time loss ARill

Another outcome variable was the frequency (%) of ARill in athletes resulting in time loss >1 day from training/competition (time loss ARill). The frequency (%) of time loss ARill is defined as the number of ARill that resulted in time loss >1 day from training or competition (numerator) divided by all the ARill (denominator), expressed as a %. This variable is reported for all ARill and in subgroups as follows: pathological classification (suspected ARinf vs. undiagnosed ARill), and anatomical classification (upper ARill/ARinf vs. general (upper/lower) ARill).

Duration of symptoms of ARill (days)

The mean duration of symptoms (days) of ARill in athletes is reported in the following subgroups: pathological classification (suspected ARinf vs. confirmed ARinf vs. undiagnosed ARill), and methods to diagnose ARinf (physician diagnosed with confirmed PCR/special investigation(s) vs. physician diagnosis by history and clinical examination vs. self-reported symptoms with algorithm). In studies reporting a specific causative pathogen for ARinf, the duration of symptoms for the common pathogens is reported (where available).

The effect of ARill on other training/competition variables

Studies reporting on the effect of an ARill on other training/competition variables were also reviewed. Variables included % of ARill resulting in training modification e.g. training reduction/discontinuation and illness burden of ARill (illness episode resulting in the inability of player to participate fully in training/competition).[38]

Data Synthesis and statistical analysis

Qualitative synthesis was performed on all 54 included articles that met the criteria for the outcome variables: days to return to sport (RTS), frequency of time loss ARill, and duration of ARill symptoms. Qualitative synthesis was also performed on other training/competition variables. The frequency (%) of time loss ARill and mean duration of symptoms (days) of ARill were estimated using a DerSimonian-Laird Binary Random effects model to account for heterogeneity in the cohorts (e.g. differences in method of diagnosis, level of athlete) and weighting of studies. Heterogeneity was measured using I^2 statistics. For frequency, analyses of the subcategories of pathological and anatomical classifications of ARill were performed. For duration of symptoms, subgroup analyses for pathological classification and by methods to diagnose ARinf were performed. Differences between subgroups were determined by comparing 95%CIs. Forest plots illustrate the results. All meta-analyses were conducted using Open Meta-Analyst. Publication bias statistics including Egger tests and funnel plots for each analysis are presented (online supplementary file 3), and were analysed using ProMeta 3. A significance level of 0.05 was accepted, and all statistical tests were two-tailed.

2.4 RESULTS

Study selection

Electronic database searches identified 767 articles. After duplicates/non-eligible articles were excluded, 68 remained and 54 met the inclusion criteria for analysis of data. Reasons for exclusion at each stage of the selection process are outlined (figure 1)

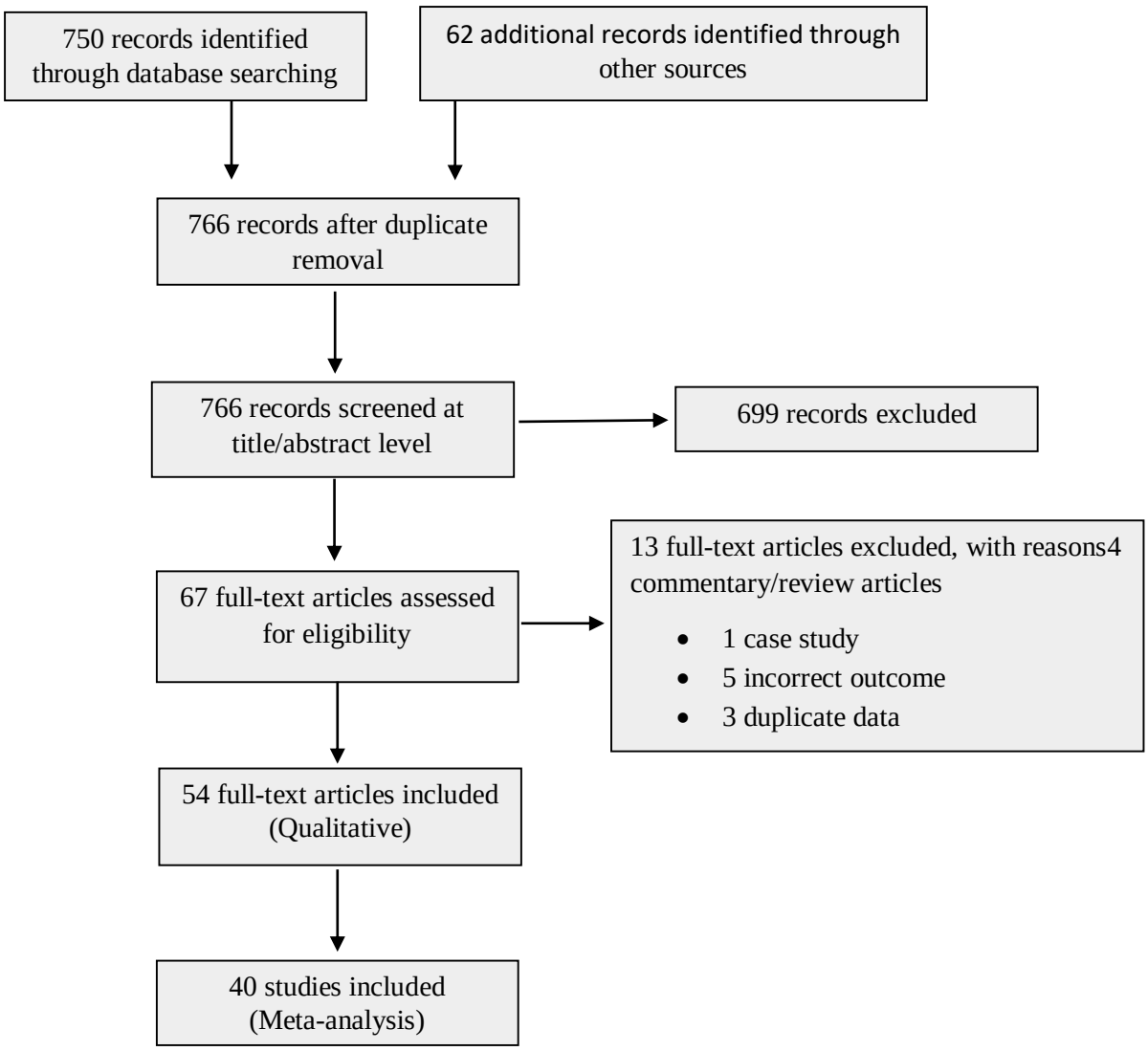

Figure 1: Study selection flow diagram

Study characteristics

Data were extracted from the 54 articles [8 9 29 38-81 52 82-88] (online supplementary table A). These studies included 31 065 athletes (including military recruits), 10 706 days of surveillance, and a sex distribution of 67% males and 33% females. No articles specifically

reported the days until RTS after ARill. Four studies reporting the number of days lost in training/competition due to ARill were included in the review, but not the meta-analysis given the small number and heterogeneity in reporting of the results. Eleven articles were included in the analysis of the frequency of time loss ARill, and 29 articles were included in the quantitative synthesis of duration of symptoms of ARill.

Level of evidence and quality assessment

The Oxford Level of Evidence for articles included in this review ranged from 1b to 3b (online supplementary table C). The modified Downs and Black quality assessment of the articles resulted in a total score ranging from a minimum score of 7 (fair) to the highest score of 13 (excellent) (online supplementary table C).

Days until return to sport (RTS)

The number of training/competition days lost due to ARill as a proxy for days until return to sport (RTS) was determined from data in 4 articles.[45 59 61 71] Training/competition days lost due to upper ARinf varied as follows: 1.7±2.3 days[59] and 3.5±5.0 days of training lost.[71] Only one study[61] reported the training/competition days lost due to lower ARinf (mean of 2.5 days per illness episode). In one study,[45] days lost were reported in two subgroups: upper ARinf and ARinf with multiple systemic symptoms (including muscle or joint pain, vomiting, diarrhoea and productive cough). In the upper ARinf subgroup, 0 days were lost, whilst in the systemic ARinf subgroup, up to 7 training/competition days were lost[45]. In two other studies,[75 76] total training/competition days lost due to ARill, accounted for 60-63% of total days with all illnesses.

Frequency (%) of time loss ARill

There were 11 unique studies[8 9 39 44-48 61 65 76] reporting the frequency of time loss ARill. These studies included 18,730 participants over 1,966 surveillance days. The estimated pooled % (95%CI) of all time loss ARill (>1 day) was 20.4% (15.3–25.4)(I^2=69.6%) (figure 2).

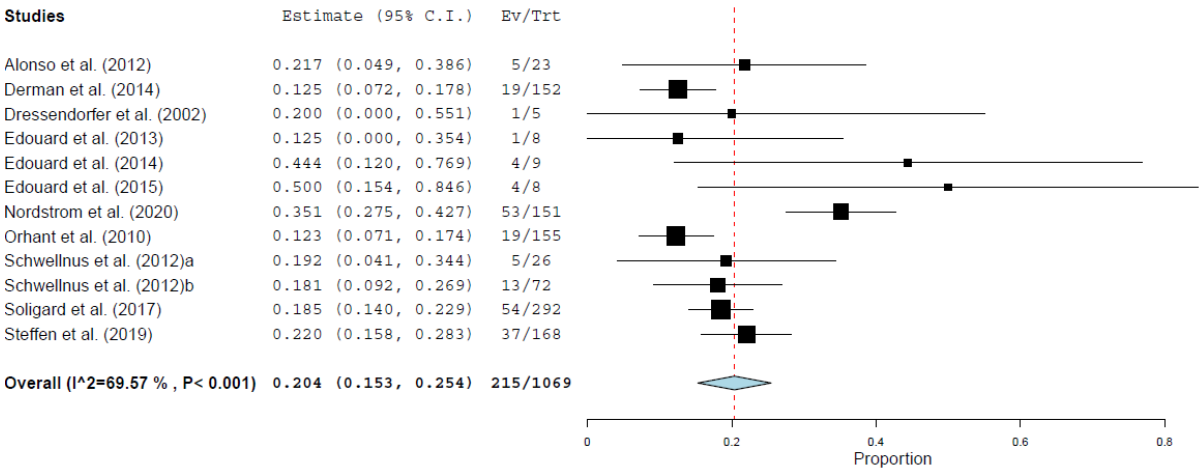

Figure 2: Frequency (%) of all time loss ARill (>1 day). The diamond shape represents the point estimate and 95% CI when an average is indicated for all the individual studies combined. Proportions are reported as %
ARill, acute respiratory illness; Ev, event=number of time loss ARill; Trt, treatment=total number of ARill

The estimated pooled % of time loss ARill was similar for suspected ARinf (17.9%; 11.8-23.9) and undiagnosed ARill (21.6%; 13.6–29.7)(I^2=69.6%) as depicted in figure 3.

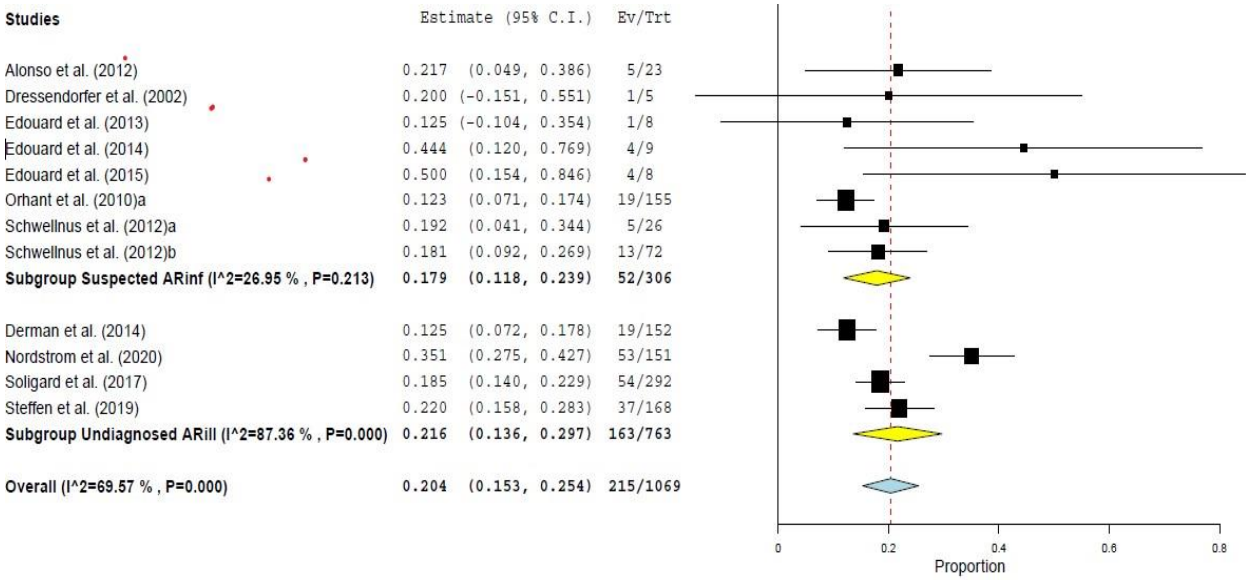

Figure 3: Frequency (%) of time loss acute respiratory illness (>1 day) by pathological classification: suspected acute respiratory infection, undiagnosed ARill. The diamond shape represents the point estimate and 95% CIs when an average is indicated for all the individual studies combined. Proportions are reported as %
Ev, event=number of time loss ARill; Trt, treatment=total number of ARill
ARill, acute respiratory illness

The number of studies distinguishing between upper and lower ARill were too few to include in the meta-analysis on % of time loss ARill. The estimated pooled % time loss ARill was similar for studies referring specifically to upper ARill (18.4%; 10.7–26.1) when compared to studies where no distinction could be made based on the anatomical classification of ARill i.e. general (upper/lower) ARill (21.3%; 14.1–28.5) (I^2=72.3%). Studies in these two groups (upper vs. general) were not combined and deemed mutually exclusive (online supplementary figure 1). There was no significant publication bias to note in the frequency analysis (online supplementary file 3).

Duration of symptoms (days) of ARill

There were 29 unique studies[29 40-42 49-60 62-64 66 68-72 67 73 74 85] that reported the duration of symptoms of ARill involving 1428 participants over 6212 surveillance days. Duration of symptoms in one study, could not be included in this analysis because of bias - as only participants with symptoms >72 hours (3 days) were included.[77] The estimated pooled mean (95% CI) duration of symptoms for all ARill was 7.1 (6.2–8.0) days.

The duration of symptoms in subgroups of ARill by pathological classification (undiagnosed ARill, suspected ARinf, or confirmed ARinf) is shown in Figure 4.

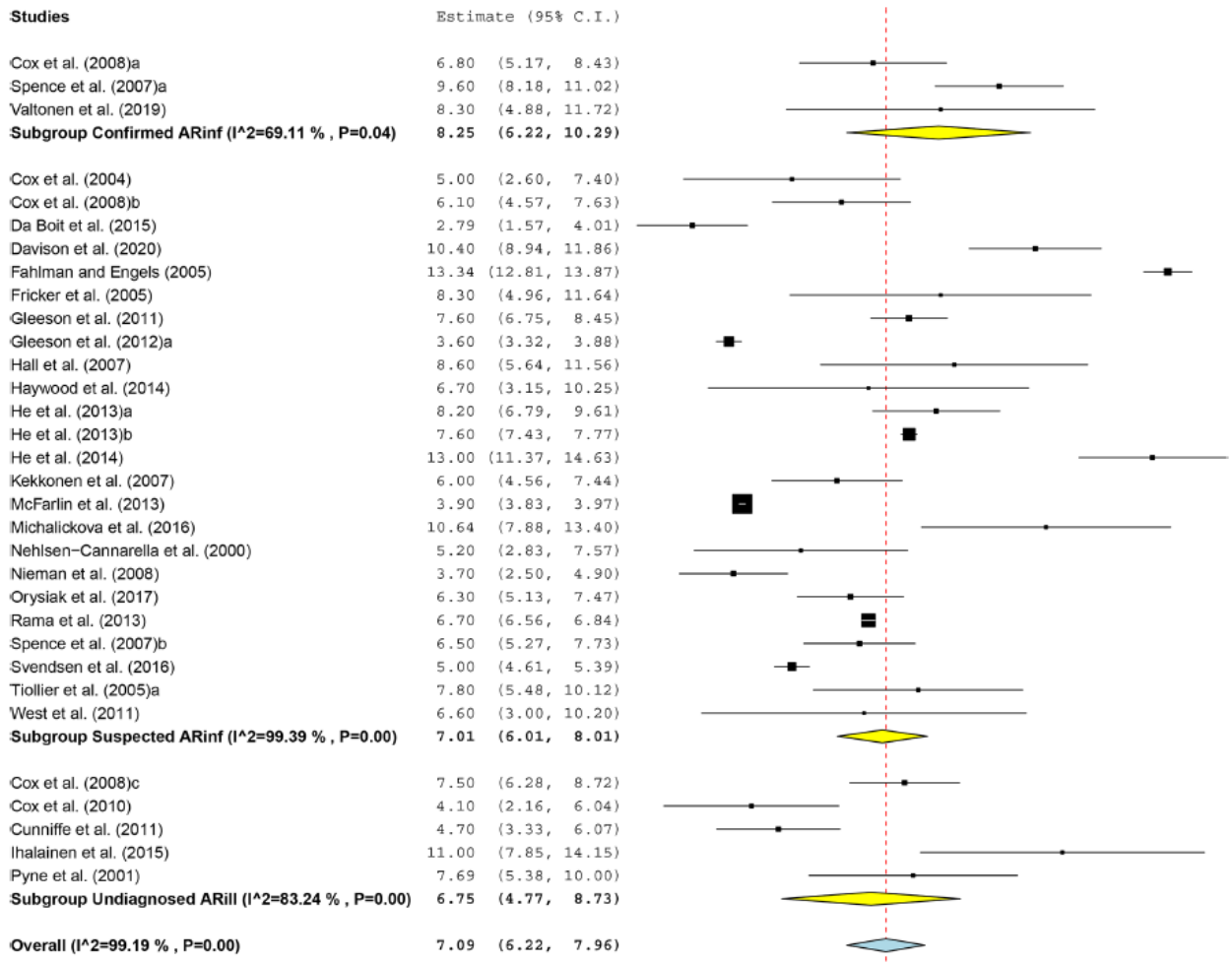

Figure 4: The duration of symptoms (days) of subgroups of ARill by pathological classification: undiagnosed ARill, suspected ARinf or confirmed ARinf. The diamond shape represents the point estimate and 95% CIs when an average is indicated for all the individual studies combined.
ARill, acute respiratory illness; ARinf, acute respiratory infection

In one study reporting ARinf, the population included both athletes and sedentary controls.[69] We included this study in the meta-analysis on symptom duration because the majority of ARinf (28/37=76%) were reported in athletes.

The estimated pooled mean (95%CI) duration of symptoms (days) of ARill of subgroups by pathological classification was similar for undiagnosed ARill (6.8: 4.8–8.7), suspected ARinf (7.0: 6.0–8.0) and confirmed ARinf (8.3: 6.2–10.3)(I^2=99.2%).

The duration of symptoms (days) of suspected ARinf (diagnosed by self-reported symptoms with algorithm and checklist) vs. suspected ARinf (physician-diagnosed by history and clinical examination) vs. confirmed ARinf (physician diagnosis with pathology confirmed by PCR, culture, or serology) are shown in figure 5.

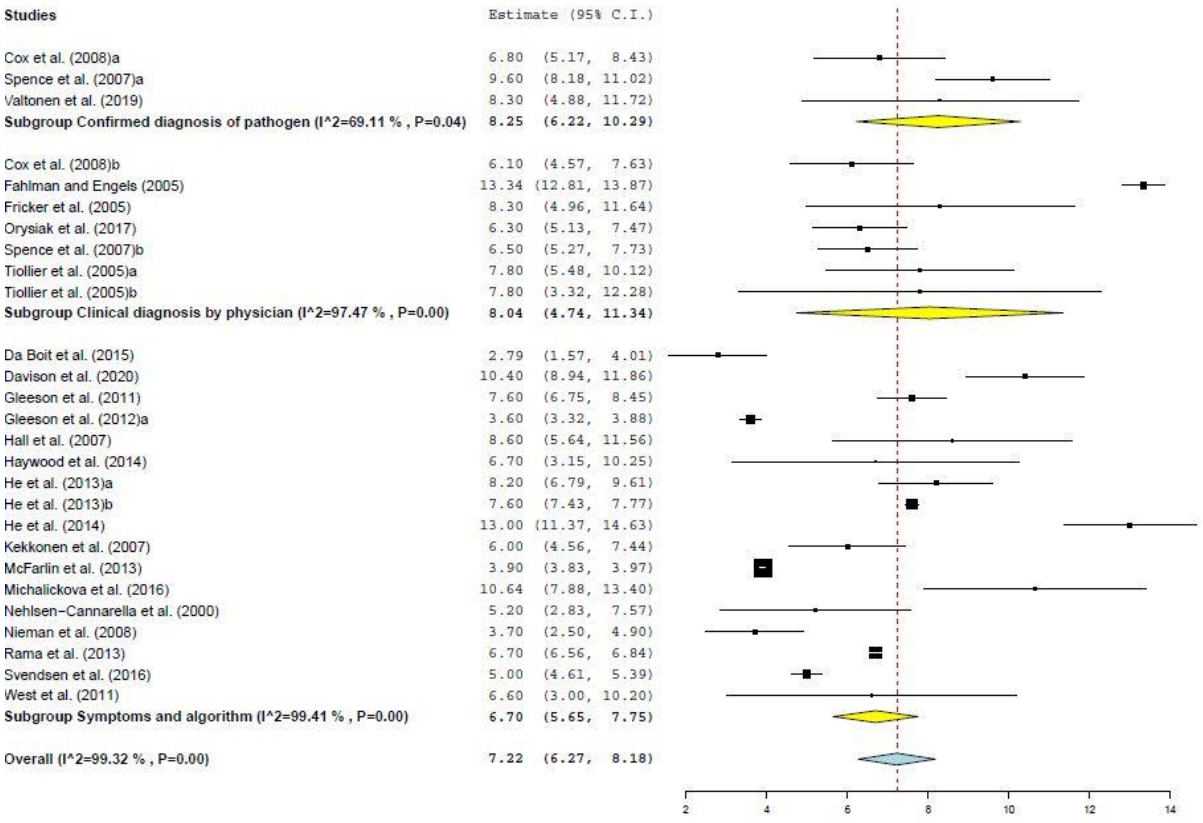

Figure 5: The duration of symptoms (days) of suspected and confirmed ARinf by method of diagnosis. The diamond shape represents the point estimate and 95% CIs when an average is indicated for all the individual studies combined
ARinf, acute respiratory infection

The estimated pooled mean (95%CI) duration of symptoms (days) of ARinf by method of diagnosis was 7.2 days (6.3–8.2) and for individual subgroups were as follows: suspected ARinf diagnosed by self-reported symptoms with algorithm and checklist (6.7; 5.7–7.8), suspected ARinf diagnosed by a physician on history and clinical examination (8.0; 4.7–11.3), and ARinf confirmed by laboratory investigation(s) using polymerase chain reaction (PCR), culture or serology tests (8.3: 6.2–10.3)(I^2=99.3%).

The duration of symptoms in athletes with confirmed ARinf was only reported in three studies.[67 69 70] In two prospective studies over several months,[69 70] a pathogen could only be identified in ~30% of ARinf. In athletes with confirmed ARinf, symptom severity and functional impairment were most severe on day 3 and 4 of illness.[69] Rhinovirus was the most common pathogen in both studies. Time loss days were not reported in these two studies. In the third study[67] of 44 athletes participating in the Winter Olympic Games, 20 athletes

presented with symptoms of the 'common cold'. A pathogen was identified in 75% of cases, and the most common pathogens causing ARinf were respiratory syncytial virus A (RSV A) followed by metapneumovirus with a mean duration of symptoms of 8.7 days and 4.0 days respectively. Both these viruses appeared in clusters within a team travelling and living together during the Games. The next most common pathogens causing ARinf were coronaviruses 229E and OC43, each with a mean duration of symptoms of 13.5 and 18.0 days respectively. In this study one athlete lost time during a competition on 1 day due to an ARinf. There was significant publication bias to note in the symptom duration analysis (online supplementary file 3).

Other outcome measures

The effect of ARill on other training/competition variables

In six studies,[38 41 55 59 70 71] the effect of ARill on selected training/competition variables was reported but variables were not standardised. The main observations from these studies were as follows: 42-70% of participants[55 59] reported that ARill negatively affected or impaired training, 14-19% of athletes[41 70] reported reduced training volume or intensity after ARill, weekly training load was reduced by 24% in athletes[55] after ARill, training was modified in up to 50% of athletes[70] after ARill, up to 31% of elite athletes[70] ceased all training during the acute phase of their ARill, and in endurance athletes, training was reduced for 3.4±5.1 days.[71] In one study over a four year period, 3.2 absence days were recorded per 1000 player-days.[38]

2.5 DISCUSSION

There are several important outcomes of this systematic review and meta-analysis. The first observation is that accurate data detailing the actual number of days to RTS after ARill in athletes are very limited. Secondly, from the best available data, approximately one in five ARill in athletes result in time loss from training/competition. Thirdly, the estimated pooled mean duration of symptoms of ARill in athletes is 7 days. Finally, for other outcome variables related to the effect of ARill on training/competition, data are very limited, but it appears that ARill negatively affects training.

Days until return to sport (RTS) after an ARill

Few studies report days lost due to ARill in athletes, duration, and types of symptoms, and the reason for time loss was not verified (due to the illness or on advice from medical or

coaching staff not to train while ill). The number of training/competition days lost due to suspected upper ARinf was reported in only four studies, and varied between 0-8.5 days.[45 59 61 71] In only one study on lower ARinf, four episodes of illness resulted in a mean of 2.5 days lost per illness.[61] Limitations of these studies are that the causative pathogen was not confirmed and the severity of infection not reported. It is likely that days until RTS after an ARinf will depend on the causative pathogen and severity of illness, as some pathogens mostly cause mild disease affecting a localised area of the respiratory tract, while others are associated with regional/systemic effects, including multi-organ involvement (moderate to severe disease). This assertion is supported by data from two recent studies on return to training (sport) after ARinf in athletes.[89 90] Both these studies could not be included in the systematic review because they fell outside the timeframe (dates) of the inclusion criteria. In the first of these studies days-until-return-to-play (sport) for subcategories of ARill were reported in rugby players over five seasons (102 738 player days). ARinf resulted in significantly more days to RTS per single illness compared with non-infective ARill ($p<0.001$) (days to RTS ratio: 10.4; 95% CI 4.3-25.3). Lower ARinf resulted in the highest number of days to RTS per single illness followed by influenza-like illness.[89] In a second study of 84 athletes with recent ARinf, athletes with confirmed COVID-19 (n=45) had more severe disease (greater number, more severe, and more prolonged symptoms), and the median days until RTS was three times longer than the subgroup with other ARinf (30 days vs. 10 days).[90] In summary, there are too few data to make firm conclusions or recommendations on days until RTS after ARill or ARinf. Limited data show that days until RTS after ARinf in athletes varied from 0-30 days and is likely dependent on multiple factors including the definition of RTS, type of sport, individual athlete factors (susceptibility to ARinf, presence of co-morbidities, immune response), the specific pathogen, and the severity of the ARinf by pathology (localised upper vs. regional lower ARinf vs. ARinf with multi-organ involvement). More studies are needed and in future we recommend accurate recording and reporting of: days until RTS, general medical history including co-morbidities, symptoms (type, duration and severity) and clinical signs, evidence of regional or systemic (multi-organ) involvement, and laboratory confirmation of specific pathogens.

Frequency (%) of time loss ARI's

There were significant limitations in the methods used in studies included in this analysis: in some studies, the decision on time loss was estimated by the physician at the time of initial presentation and therefore not confirmed, in most cases the specific diagnosis and the

causative pathogen was not confirmed, and in several studies the predominant anatomical area (upper or lower respiratory tract) affected by the ARill/ARinf was not clear. The main observation is that the % of time loss ARill (illness episodes resulting in time loss >1 day from training or competition) is low (20%) and accordingly, by inference, that the large majority (i.e. 80%) of ARill are not severe, because they are associated with no time loss. The % of time loss ARill was similar in subgroups based on the pathological and anatomical classification (suspected ARinf 17.9%; undiagnosed ARill 21.6%; upper ARill 18.4%; general (upper/lower) ARill 21.3%). Although the low % of time loss ARill indicates that most ARill are not severe, there are data from other studies that clearly show a significant burden (a measure of both severity and incidence) of acute illness in athletes, particularly ARill/ARinf.[43 76 91] Future studies in this area are needed, addressing these limitations.

Duration of symptoms of ARill (days)

The mean symptom duration of any ARill in athletes was 7 days. The duration of symptoms of ARill was similar in subgroups based on the method used to diagnose ARinf: suspected ARinf diagnosed by self-reported symptoms with algorithm and checklist (6.7 days), suspected ARinf diagnosed by a physician on history/clinical examination (8.0 days) and confirmed ARinf by laboratory investigations (8.3 days). The duration of symptoms results must be interpreted with caution due to the large heterogeneity in data (I^2>99%). In two studies, the pathogen could only be identified in ~30% of ARinf [69 70] and the most common pathogen in these studies was rhinovirus. This is also the most common pathogen causing ARinf in the general population.[92 93] A study[67] on Finnish athletes participating in the 2018 Winter Olympic Games, identified the causative pathogen in 75% of cases of ARill. The pathogens occurred in clusters of athletes travelling and living together and this might differ from the normal distribution of pathogen occurrence. In one study,[70] participants with confirmed upper ARinf the duration of symptoms was 6.8±3.8 days. In suspected ARinf (PCR/culture negative but abnormal full blood count) the duration was 6.1±3.4 days, and in the ARill subgroup (negative PCR and normal laboratory investigations) the duration of symptoms was 7.5±3.4 days. In our review, data on duration of symptoms in athletes with confirmed ARinf were therefore limited to a few specific pathogens that cause ARinf: rhinovirus, respiratory syncytial virus (RSV) or coronaviruses (229E and OC43).[67 69 70]

A further limitation in all the studies documenting symptoms is that the duration of specific or regional symptoms of ARill were not reported. To distinguish between symptoms is

important in clinical RTS decision making[90] e.g. rhinorrhoea (localised) as the only symptom may not prevent RTS, while the presence of chest pain (regional) or generalised myalgia (systemic) might delay RTS. There are data from three recently published studies (not included in the systematic review as they were published outside the time frame) documenting symptom duration in athletes infected with the specific pathogen (SARS-CoV-2) causing COVID-19. In a case series of 90 athletes with confirmed COVID-19, 23% were asymptomatic and 77% mildly symptomatic. The mean (±SD) duration of symptoms in the mildly symptomatic subgroup was 9±14 days.[94] In another study, symptoms of "mild" COVID-19 lasted <1 week in a group of 15 symptomatic football players.[95] In the third study, individual and regional symptom duration was reported in 84 athletes with ARinf (45 confirmed COVID-19, and 30 suspected ARinf).[90] This is the first study to report duration of specific individual symptoms in athletes with ARinf. For all the athletes with ARinf (n=84) the duration (median days) of symptoms was: localised (nose and throat) symptoms (9-10 days), regional (chest and neck) symptoms (14 days), and systemic symptoms (11 days). In this study, specific individual symptoms, and a particular symptom cluster, were associated with more prolonged return to training.[90] This symptom cluster also included symptoms "above the neck" such as headache and altered/loss sense of smell. These symptoms were, together with "excessive fatigue" and "fever / chills" significantly related to prolonged return to training. These early data do not support the "neck check" as a clinical tool for RTS decision making. In future studies, we recommend accurate recording and reporting of the duration and severity of each specific symptom, regional symptoms (such as localised, regional or systemic symptoms), as well as the specific pathogen causing an ARinf.

The effect of ARill on other training/competition variables

The effect of ARill on training could not be analysed due to small number of studies with heterogeneous reporting of results. However, from six studies[38 41 55 59 70 71] reporting on the effects of ARill on training, it is evident that an ARill potentially has a negative impact on the ability to continue with a regular training schedule. The reason/s for modification/cessation of training was not recorded and may relate to several factors including: the direct consequence of the illness process, symptoms (type, duration, severity), decrease in exercise/sporting performance directly due to the pathology of an acute infection, and advice by medical personnel or coaching staff to modify training intensity or not to train at all.

Strengths and limitations

To our knowledge, this is the first systematic review to determine the effects of ARill on RTS in athletes. We registered the review with PROSPERO and followed a systematic approach using an online tool, CADIMA. We developed a classification system, based on methods to diagnose an ARill, and performed analyses using a pathological and anatomical classification. We believe this approach provides a more comprehensive clinical picture to inform management strategies and RTS protocols. This review has clinical importance and relevance given that ARill is the most common illness affecting athletes resulting in time loss.

The main limitations of this systematic review are related to the studies that could be included. Although we included 54 studies, these were only in the English language, and did not include recently published studies related to the COVID-19 pandemic as these fell outside the pre-defined timeframe of the review. There is also a potential risk of publication bias that we cannot account for. Egger's tests and funnel plots indicated a higher risk for publication bias for the duration of symptoms results, compared to the prevalence of time loss data. Among studies that were included, there was inconsistency in the definition and reporting of outcome variables and heterogeneity in athletic populations studied. There was no consensus on pathological and anatomical classification and definition of ARill subgroups. We could only include a small sample of studies that reported outcome variables in subgroups e.g. confirmed ARinf. We also acknowledge that one of our outcome variables, the duration of symptoms, does not necessarily predict days until return to sport after an ARill. Finally, in most studies reporting the % of time loss ARill, this was an estimated time loss ARill that physicians recorded at the time of initial diagnosis, and not necessarily verified.

The risk of publication bias was difficult to assess given poorly defined outcome variables to measure RTS and the heterogeneous methods and reporting of results. The I^2 results (I^2>99% for duration of symptom analyses), indicates the high level of heterogeneity, and although effort was made to categories ARill in subgroups, the results were still varied. The authors acknowledge the impact this might have on the research findings. A uniform approach to the definition of variables, methods to diagnose ARill, and classification of ARill in the athletic setting is needed. In this review we propose such classifications. We believe this framework will assist both clinicians and researchers to better characterise variables and their time

course. This approach is important for development of evidence-based guidelines on RTS in athletes with ARill.

2.6 SUMMARY AND CLINCIAL IMPLICATIONS

Respiratory illnesses are common in athletes, but to make an accurate pathological diagnosis is challenging and costly. An ARill in the athlete raises two major clinical concerns; first, the athlete and coach are concerned about the athlete's ability to train and perform, and secondly, the SEM physician is required to provide safe RTS guidelines for an athlete after an ARill. In this systematic review and meta-analysis, we identified that ~20% of ARill resulted in more than one day of time loss from training. The mean duration of symptoms of ARill was 7 days, regardless of pathological (infective vs. undiagnosed), anatomical (upper vs. general) classification, or subcategories based on the method used to diagnose ARinf. In a few studies where individual and regional symptoms were recorded and a specific pathogen causing the ARinf identified, there was considerable variability in the duration of symptoms of the ARinf. Moreover, there is early evidence that discrete symptoms that are both "above" and "below" the neck, as well as subgroups of ARinf are associated with more prolonged time to RTS. This individual variability highlights the fact that future studies are needed where days until RTS, individual and regional symptoms (and severity of symptoms) are accurately recorded and reported in athletes with a confirmed diagnosis of ARinf (pathogen identified). This information will refine future RTS clinical decision making, which we anticipate will be highly customized and based on the individual athlete response to infection from a specific pathogen that causes ARinf.

What is already known?

- Acute respiratory illness (ARill) is the most common illness affecting athletes, and these are mostly acute respiratory infections (ARinf)
- ARill can result in time loss from training and competition
- Return to sport (RTS) criteria after ARill in athletes are largely based on broad criteria related to symptoms "above" or "below" the neck

What are the new findings?

- The actual days to RTS after ARill is under researched and not well documented, with large individual athlete variation
- The majority of ARill do not result in >1 day of time loss from training or competition
- The mean symptom duration of an ARill in athletes is 7 days (both ARinf and other ARill of unknown cause)
- ARinf and ARill can have a negative impact on ability to train and compete
- In clinical practice and for future studies, we recommend a standardised approach to:
    - the classification and definition of ARill/ARinf
    - method of diagnosing ARill/ARinf
    - uniform approach to documentation of both individual and regional symptoms of ARill/ARinf
    - accurate recording and reporting of outcome variables (return to sport, physical signs, laboratory confirmation of pathogen(s) causing ARinf)

Contributorship

Conceptualisation: CS, DP, NS, MS, KK, JH. Methodology: CS, DP, NS, MS. Writing and original draft: CS, DP, MS, NS. Writing, review, and editing: CS, DP, NS, MS, KK, JH

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Competing interests

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Patient consent for publication

Not applicable

Provenance and peer review

Not commissioned; externally peer reviewed

Supplementary documents

Files

Online supplementary file 1: Specific search strategies

Online supplementary file 2: Modified Downs and Black Quality Assessment Checklist

Online supplementary file 3: Publication statistics - Egger's test and Funnel plots

Tables

Online supplementary table A: Summary of articles - data extraction of the demographics

Online supplementary table B: Summary of articles - data extraction by classification and outcomes

Online supplementary table C: Modified Downs and Black score and Oxford Level of Evidence

Figures

Online supplementary figure 1: Frequency (%) of time loss ARill >1 day by anatomical classification: upper ARill vs. general (upper/lower) ARill

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In Chapter 2, RTS parameters i.e. days to return to sport (RTS), frequency (%) of time loss suspected and confirmed ARill, and duration of symptoms were explored in a systematic review with meta-analysis. This review was commissioned before COVID-19 was declared a global pandemic (March 2020). RTS parameters in SARS-CoV-2 were thus unknown.

In Chapter 3, a chronological approach is taken to review available data on RTS parameters as the COVID-19 pandemic progressed. Data are divided into 3 domains: 1) expert opinion *before* original research became available, 2) expert opinion *after* original research became available, and 3) original research. The outcome variables in each domain are summarised and discussed.

This narrative review thus serves to compliment the findings of the systematic review and meta-analysis described in Chapter 2 to identify knowledge gaps on RTS parameters in an athlete with a recent ARinf, including SARS-CoV-2.

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CHAPTER 3

Acute SARS-CoV-2 infection and return to sport in athletes: A narrative review

3.1 BACKGROUND

In Chapter 1, the impact of SARS-CoV-2 on athletes' health, the concept of time loss due to acute respiratory infection (ARinf), and the continuum of return to sport (RTS) after infection, were described. Chapter 2 reports the findings of a systematic review undertaken to determine the effects of acute respiratory illness (ARill) on RTS. The focus of the systematic review was on the duration (days) to return to training, prevalence of time loss ARill, and duration symptoms during the acute phase of ARill in athletes.

This systematic review described in Chapter 2 commenced in March 2019, at the beginning of this PhD thesis. The first cases of COVID-19, caused by SARS-CoV-2 infection, were reported in December 2019. This virus spread rapidly across the globe in the first few months of 2020, and was officially declared as a pandemic on 11 March 2020 by the World Health Organization (WHO).[1] The cut-off time for inclusion of original research studies for the systematic review described in Chapter 2, was 31 July 2020. At that time, there were no original research studies published on RTS after COVID-19. Therefore, data on RTS parameters and factors associated with RTS after SARS-CoV-2 infection in athletes, were not available.

In the early phases of the progression of the COVID-19 pandemic, several manuscripts were published recommending the duration (days) before return to training (RTT), as well as screening protocols and guidelines for medical clearance before RTT after a recent SARS-CoV-2 infection. However, these were expert opinions because no original data were available. The novelty of SARS-CoV-2, the fear for adverse medical outcomes and the lack of knowledge, all had a potential impact on RTT recommendations.

The first original research studies on SARS-CoV-2 in athletes focused mainly on the clinical and laboratory findings of cardiovascular involvement.[2-8] As cardiovascular complications can have potential serious and detrimental outcomes, screening protocols were also focused

on cardiac testing, and the cardiac triad (i.e. electrocardiogram, echocardiogram and high sensitivity cardiac Troponin T) was proposed.[9-12]

At this time, several unique factors influenced advice and recommendations on the RTS decision after SARS-CoV-2 infection in athletes. Firstly, the advice on time (days) to return to training was not necessarily determined by the clinical parameters of the infection, but also by international and national public health regulations on proposed isolation periods of SARS-CoV-2 positive individuals. In addition, sports federations and organisations also dictated isolation periods and provided athletes with advice on the duration to refrain from training. Secondly, certain SARS-CoV-2-related medical conditions resulted in a specified period of recommended time (days) before return to training e.g. athlete with myocarditis was advised not to participate for 3 to 6 months. Differentiation between factors delaying resumption of training, were mostly not reported. Thirdly, the frequency (%) of time loss ARinf could not be established for SARS-CoV-2, because most athletes were advised to isolate and abstain from training for a varying duration during the acute phase of the infection. Finally, during the pandemic, SARS-CoV-2 infection could not always be confirmed by laboratory testing due to limitations in testing capacity and availability at national, institutional or individual level. Although the majority of studies included confirmed SARS-CoV-2 infections,[13-16] there were some studies that reported findings on suspected infection.[17 18]

To our knowledge, the first original research study on RTS parameters in athletes after SARS-CoV-2 infection, was reported in February 2021.[13] Since then, limited original research studies were published on: 1) actual days to return to training after SARS-CoV-2 infection, 2) duration and number of SARS-CoV-2 symptoms during the acute phase of the infection, and 3) factors that may affect RTT in athletes after SARS-CoV-2 infection. To date (November 2022), there are no published studies reporting on days returning to pre-infection sports performance i.e. return to full performance, after SARS-CoV-2 infection in athletes.

The main aim of this chapter is to review the literature on acute SARS-CoV-2 infection and return to sport in athletes. This review will complement and follow on the systematic review described in Chapter 2. A novel approach of this review will be to describe the chronological order of how scientific information on RTS after SARS-CoV-2 infection in athletes became available during the COVID-19 pandemic in three domains. The three domains are based on

the type of study (original research vs. other publications - editorials/expert opinion/consensus statements/reviews/special communications) and the date of publication of the first original research study on RTS after SARS-CoV-2 infection in athletes.
This review specifically focuses on the following outcome variables related to SARS-CoV-2 infection in athletes: 1) recommended time (days) before RTT, 2) medical screening protocols and clearance before RTT, 3) recorded actual time course (days) for RTT, 4) symptom duration during the acute phase of infection, 5) number of symptoms during the acute phase of infection, and 6) factors associated with time to RTT. This review will identify specific knowledge gaps on RTS in athletes after SARS-CoV-2 infection, some of which will are addressed in subsequent chapters of this thesis.

3.2 METHODS

Search strategy

A narrative review was conducted on articles mainly identified in PubMed and EBSCOhost database searched up to 20 October 2022. The search terms used were athlete* AND (COVID-19 OR SARS-CoV-2). Studies were selected if they contained relevant and non-repetitive information on outcome measures. Additional articles were identified by hand searching references and other electronic resources. The literature was explored for both review/editorial articles as well as original research written in English.

Study selection and eligibility criteria

Inclusion criteria for review/editorials articles were:

1) Editorials, expert opinion, consensus statements, reviews and special communications
2) Athletes >18 years old participating in any level/type of sport
3) SARS-CoV-2 infection suspected or confirmed
4) Review/editorials that included duration (days) recommended before RTT for asymptomatic, mild, moderate or severe SARS-CoV-2 infection and/or screening protocols for asymptomatic, mild, moderate or severe SARS-CoV-2 infection

Inclusion criteria for original research journal articles were:

1) Original research articles
2) Athletes >18 years old participating in any level/type of sport
3) SARS-CoV-2 infection suspected or confirmed

4) Actual duration (days) to RTT after recent SARS-CoV-2 infection
5) Symptom duration during acute phase of SARS-CoV-2 infection
6) Number of symptoms during acute phase of SARS-CoV-2 infection
7) Factors influencing time to RTT after SARS-CoV-2 infection in athletes

Single case studies were not included.

Outcome variables

The six outcome measures in this review are defined as follows:

1. *Recommended time (days) to RTT:* The recommended days before training should be resumed by expert opinion.
2. *Return to sport screening protocols:* A list of screening tests recommended before RTT, and indications for each test, were reviewed for asymptomatic, mild, moderate or severe infections.
3. *Actual days to RTT:* The actual days from the date of diagnosis or onset of symptoms of SARS-CoV-2 infection to RTT from original research publications. This is measured as days to RTT [mean (SD), mean (95%CI) of median (IQR)].
4. *Symptom duration:* The number of days from the onset of symptoms to the resolution of symptoms [mean (SD) or median (IQR)].
5. *Number of symptoms:* The number of symptoms per athlete during the acute phase of SARS-CoV-2 infection (mean, 95%CI).
6. *Factors associated with time to RTT*: Any factors that may be associated with prolonged days to RTT.

Chronological order of reporting results in three domains

The presentation of results will be in three domains, based on: 1) the type of publication (editorials/expert opinion/consensus statements/reviews vs. original research), and 2) the date of publication of the first original research study on RTS after SARS-CoV-2 infection in athletes (February 2021)

1. Editorials/expert opinion/consensus statements/reviews and special communications on time (days) to return to training and/or screening protocols *up to and including* February 2021.
2. Editorials/expert opinion/consensus statements/reviews and special communications on time (days) to return to training and/or screening protocols *after* February 2021.

3. Original research studies published *after* February 2021 reporting actual duration (days) to RTT, symptom duration, number of symptoms and/or factors associated with time to RTT.

3.3 RESULTS

Domain 1: Editorials/expert opinion/consensus statements/reviews/special communications on time (days) to return to training and/or screening protocols up to and including February 2021

Editorials, expert opinions, consensus statements, reviews or special communications that reported recommended duration (days) before RTT, and/or included screening protocols for asymptomatic, mild, moderate or severe SARS-CoV-2 infection in athletes were explored. This body of literature was published before the first original research data on RTS in athletes became available (2020 to February 2021). In this period, there were no original studies on RTS. Therefore, only outcome variables 1 and 2 could be derived from these publications and 9 of these articles are summarised in Table 1.

Table 1: Editorials, expert opinions, consensus statements, reviews or special communications on recommended time (days) before return to training and/or screening protocols for asymptomatic, mild, moderate or severe SARS-CoV-2 infections before the publication of original RTS research (2020 up to/including February 2021)

Author/s, year	Type of study	SARS-CoV-2 severity	Outcome variable 1: Recommended time (days) before return to training	Outcome variable 2: Return to sport screening protocols
Phelan D et al[9] (May 2020)	Special communication	Asymptomatic	≥ 2 weeks from positive SARS-CoV-2 test	Follow appropriate clinical pathway if clinical and/or cardiac symptoms develop
		Mild/moderate	≥ 2 weeks after symptom resolution	Clinical evaluation, 12 lead ECG, echocardiogram, laboratory tests. Additional symptom-guided testing should be considered
		Severe	≥ 2 weeks after symptom resolution	Cardiac imaging should be considered
Schellhorn P et al[19] (May 2020)	Review	Asymptomatic	No intense/competitive exercise for 2 weeks	Resting ECG
		Mild/moderate	Sport restriction 2-4 weeks	Testing according to severity: Resting/exercise ECG or echo as indicated
		Severe	Suspected myocarditis - follow appropriate recommendations	If suspected myocarditis - follow appropriate diagnostic testing
Bhatia RT et al[10] (June 2020)	Consensus statement	Asymptomatic	7 days from positive SARS-CoV-2 test, resume systematic exercise if no symptoms on day 7	Consider individual demographics/ comorbidities. No routine testing
		Mild	7 days after symptom resolution	Consider Trop T, CRP, if abnormal do ECG; CMR; ECHO, ECG monitoring
		Moderate/severe	7 days after symptom resolution if no cardiac involvement	Consider Trop T, CRP, if abnormal do ECG; CMR; ECHO, ECG monitoring
Baggish AL et al[11] (June 2020)	Editorial	Asymptomatic	NR	Focused medical history and physical examination. Consider 12-lead ECG. If abnormal, do ECHO and exercise test
		Mild	NR	Same as asymptomatic and ECG
		Moderate/severe	NR	12-lead ECG, ECHO, exercise testing, ambulatory rhythm monitoring, blood and biomarkers
Santos-Ferreira et al[20]	Review	Asymptomatic	NR	Physical examination, if abnormal, additional testing according to clinical presentation and severity

(Sept 2020)		Mild/moderate/severe	≥ 7 days from symptom resolution	Physical examination, if abnormal, additional testing according to clinical presentation and severity
Wilson MG et al[12] (Sept 2020)	Review	Recovered	>10 days since onset of symptoms and 7 days symptom free	Physical examination, resting ECG and ECHO, if abnormal CMR ± 24-hour Holter monitoring, Trop T, CPET
		Not recovered > 14 days since symptom onset	>10 days since onset of symptoms and 7 days symptom free	Physical examination, ECG, CMR, CXR, spirometry, Trop T, D-Dimer, CRP
		Hospitalised	NR	Physical examination, ECG, CMR, 24-hour Holter monitoring, CPET, CXR, Trop T, D-Dimer, CRP
Udelson JE et al[21] (Oct 2020)	Editorial	Asymptomatic/mild	NR	No risk stratification. Monitoring for cardiovascular symptoms once activity is resumed
		Moderate/severe	NR	Risk stratification. Monitoring for cardiovascular symptoms once activity is resumed
Kim JH et al[22] (Oct 2020)	Review	Asymptomatic	10 days from SARS-CoV-2 positive test	Individualised, follow clinical pathway for new or cardiac symptoms
		Mild	10 days from onset and full symptoms resolution	Individualised, follow clinical pathway for new or cardiac symptoms
		Moderate	10 days after resolution of symptoms	Medical evaluation, ECG, ECHO, laboratory tests. If abnormal: CMR, exercise test and extended ambulatory rhythm monitoring
		Severe	14 days after resolution of symptoms	Laboratory test and cardiac imaging during hospitalisation
McKinney J et al[23] (Nov 2020)	Position statement	Asymptomatic	NR	Medical history and physical examination. Consider ECG and Trop T if new cardiac symptoms/marked reduction in fitness
		Mild/moderate/severe	7 days after resolution of symptoms	Medical history and physical examination. Consider ECG and Trop T if new cardiac symptoms/marked reduction in fitness

NR, not reported; ECG, electrocardiogram; ECHO, echocardiogram; CMR, cardiac magnetic resonance; Trop T, Troponin T; CPET, cardiopulmonary exercise test; PPE, pre-participation evaluation; CXR, chest x-ray; CRP, C-Reactive Protein

Outcome variable 1: Recommended time (days) to RTT

The recommended days before RTT varied considerably during the first year (2020) of the pandemic ranging from a time period between one[10] and four weeks.[19] This duration also depended on either a fixed period from positive SARS-CoV-2 test/onset of symptoms[19] or time from the resolution of symptoms.[10 12 20 22] In a consensus statement by experts in sports

cardiology, 7 days of rest was recommended for asymptomatic athletes, or 7 days from resolution of symptoms was advised once cardiac involvement was excluded.[10]

Outcome variable 2: Return to sport screening protocols

Screening protocols were diverse for all severity groups. Testing on asymptomatic athletes included no routine testing,[9 10] standard cardiac screeing,[12 19] testing according to abnormalities found on physical examination,[20] or selective testing if cardiac symptoms[21 22] or marked fitness reduction[23] was observed once training resumed. Suggested screening for mild to severe cases were mostly standardised screening protocols,[9-12] but the concept of testing guided by abnormal physical findings[20 23] or additional symptom-guided testing[21] was introduced. The focus of all the screening protocols was on the cardiovascular system, and occasionally respiratory system, with little regard for other organ systems.

Domain 2: Editorials/expert opinion/consensus statements/reviews/special communications on time (days) to return to training and screening protocols after February 2021

There were several expert opinions, editorials, consensus statements, special communications and reviews after February 2021 that reported on recommended duration (days) before RTT, and/or screening protocols for asymptomatic, mild, moderate or severe SARS-CoV-2 infection in athletes. The outcome variables (outcome variable 1 and 2) derived from five publications are summarised in Table 2.

Table 2: Editorials, expert opinion, consensus statements, reviews or special communications on recommended time (days) to return to training and/or screening protocols for asymptomatic, mild, moderate or severe SARS-CoV-2 infections after the first original RTS research publication (March 2021-October 2022)

Author/s, year	Type of study	COVID-19 severity	Outcome variable 1: Recommended time (days) before RTT	Outcome variable 2: Return to sport screening protocols
Ross R et al[24] (May 2021)	Special communication	Asymptomatic	≥ 10 days	ECG, ECHO, Trop T, screen athletes with co-morbidities. Monitor when training resumes
		Mild/moderate/ severe	≥ 10 days and symptom resolution	ECG, ECHO, Trop T, screen athletes with co-morbidities. Monitor when training resumes
		Mild/moderate/ severe	≥ 10 days and symptom resolution	ECG, ECHO, Trop T, screen athletes with co-morbidities. Monitor when training resumes
Vasiliadis AV et al[25] (Aug 2021	Special communication	Asymptomatic	>14 days	NR
		Mild	No exercise 2 weeks, close monitoring	Comprehensive clinical evaluation, ECG, ECHO, Trop T, CRP and cardiac biomarkers, brain natriuretic peptide as clinically indicated
		Moderate/severe	No exercise till cardiac clearance	Cardiology investigation with cardiac biomarkers, spirometry, CXR, medical team-based approach with Holter, CMR, chest CT
Gluckman TJ et al[26] (March 2022)	Consensus statement	Asymptomatic	3 days	If non-cardiac symptoms, no testing
		Mild/moderate	Resolution of non-cardiac symptoms	If non-cardiac symptoms, no testing
		Severe	After cardiology consultation clearance	Cardiopulmonary symptoms or suspicion of cardiac involvement (chest pain/pressure, dyspnoea, palpitations, syncope) do ECG, ECHO, Trop-T. If abnormal do additional testing e.g. CMR
Baggish AL et al[27] (May 2022)	Special communication	Asymptomatic	NR	Standard pre-participation cardiovascular screen, symptom-orientated additional tests if indicated
		Mild/moderate	Resolution of acute symptoms	Standard pre-participation cardiovascular screen, symptom-orientated additional tests if indicated
		Severe	Restriction pending cardiac consultation	Hospitalised/myocarditis syndrome: Cardiac evaluation and/or cardiology consult
	Review	Asymptomatic	3 days from positive SARS-CoV-2 test	Clinical testing only if cardiopulmonary symptoms develop

O'Conner FG et al[28] (Nov 2022)		Mild	3 days from symptom onset and symptoms resolved	Clinical testing only if cardiopulmonary symptoms develop
		Moderate	If no cardiopulmonary symptoms, 5 days plus symptoms resolution	Clinical testing only if cardiopulmonary symptoms develop
		Severe (or cardiopulmonary symptoms)	NR	ECG, biomarkers, ECHO. Refer to cardiology

RTT, return to training; NR, not reported; ECG, electrocardiogram; ECHO, echocardiogram; Trop T, Troponin T; CRP, C-reactive protein; CXR, chest x-ray; CMR, cardiac magnetic resonance; Chest CT, chest computerized tomography

Outcome variable 1: Recommended time (days) to RTT

The main observation from studies published in this domain is that the recommended time before RTT after SARS-CoV-2 infection in athletes ranged from 10-14 days[24 25] when compared to domain 1 (1-4 weeks). The recommended days to RTT became substantially shorter in 2022 compared with 2021, with the emphasis on the resolution of acute[27] or cardiac-related symptoms.[26 28]

Outcome variable 2: Return to sport screening protocols

As the pandemic progressed, RTS screening protocols and guidelines still varied considerably. In 2021 standard cardiac screening was mostly recommended[25] but as time progressed, this was replaced by testing that was guided by the presence of cardiopulmonary symptoms,[26 28] suspicion of cardiac involvement[26] or standard pre-participation cardiovascular screening with additional symptom-orientated testing.[27] However, the main emphasis of screening protocols was still on the resolution of cardiac symptoms and cardiac clearance.

Domain 3: Original research studies on actual duration (days) to RTT, symptom duration, number of symptoms and factors associated with time to RTT (February 2021 to October 2022)

There were six original research articles that reported the actual duration (days) to RTT, symptom duration and number of symptoms during the acute phase of infection, and/or factors associated with time to RTT (outcome measures 3, 4, 5 and 6) and these are summarised in Table 3.

Table 3: Original research on actual duration (days) to RTT, symptom duration, number of symptoms and factors associated with prolonged RTT in SARS-CoV-2 infections (March 2021-October 2022)

Author/s, year	Type of study, number SARS-CoV-2 + participants	Sport level and type	Outcome variable 3: Days to RTT	Outcome variable 4: Symptom duration	Outcome variable 5: Symptom number	Outcome variable 6: Factors associated with prolonged RTT
Schumacher YO et al[13] (Feb 2021)	Prospective cohort, n=36	Professional football	NR	<7 days (except loss smell/taste)	NR	NR
Schwellnus MP et al[18] (March 2021)	Cross-sectional descriptive, n=45	Competitive, mixed	Median 30 days (95%CI:16-40)	Median days (95% CI) reported for 26 individual symptoms	Mean 10.4 (95%CI: 8.9-12.1)	Symptom cluster associated with prolonged RTT: Excessive fatigue, chills, fever, headache, altered /loss sense of smell, chest pain/pressure, difficulty in breathing and loss of appetite
Cavigli L et al[14] (May 2021)	Prospective cohort, n=94	Competitive, mixed	NR	Mean (SD) 9±14 days	NR	NR
Krzywański J. et al[15] (July 2021)	Prospective, n=111	Elite, mixed	NR	At screening time (median 20 days since diagnosis of infection): those with symptoms had symptom duration (mean SD) of 7.5 ± 4.2 and those without symptoms 5.0 ± 3.9 days	NR	NR
Hull JH et al[17] (Aug 2021)	Retrospective case, n=147	Elite, mixed	Median 18 days (IQR: 12-30)	Median (IQR) 10 (6-17)	NR	Specific symptoms: Chest pain associated with prolonged time loss (>28 days).

						Athletes with lower respiratory symptoms 2.1 (CI 1.2-3.5) times more likely to have prolonged time loss (>28 days)
Petek BJ et al[16] (Nov 2021)	Observational cohort, n=3597	Collegiate, mixed	Median 17 days (IQR: 13–21	NR	NR	NR

RTT, return to training; NR, not reported; CI, confidence interval; IQR, interquartile range; SD, standard deviation

Outcome variable 3: Actual days to RTT

The actual recorded duration (days) for an athlete to return to training was only recorded in 3 studies. The median days to RTT ranged from 17-30 days.[16-18]

Outcome variable 4: Symptoms duration during the acute phase of infection

There were five original research studies reporting the duration of symptoms. Symptom duration was mostly recorded for individual symptoms,[18] whilst combined symptom (symptom group) duration was reported heterogeneously. The duration of symptoms ranged from < 7 days (with the exception of loss of smell or taste) in elite football players,[13] 9±14 (mean; SD) for competitive athletes in different sport types,[14] or 5.0 ± 3.9 to 7.5 ± 4.2 (mean;SD) in a group of mixed elite athletes.[15] In a collegiate cohort, symptom duration was a median of 10 days (IQR: 6-17).[17]

Outcome variable 5: Number of symptoms during the acute phase of infection

The mean number of symptoms per participant during the acute phase of infection was recorded in only one study as 10.4 (95%CI: 8.9-12.1).[18]

Outcome variable 6: Factors associated with time to RTT

Factors associated with prolonged time (more days) to RTT was reported only in two studies. The main findings of these two studies were: 1) that specific symptoms and symptoms clusters (excessive fatigue, chills, fever, headache, altered/loss sense of smell, chest pain/pressure, difficulty in breathing and loss of appetite) were associated with prolonged RTT,[18] and 2) that athletes with lower respiratory symptoms were twice more likely to have prolonged time loss (>28 days).[17]

3.4 DISCUSSION

The main findings of expert opinions before and after the publication of original research (domain one and two) were: 1) Suggestions on the recommended time (days) to RTT varied greatly throughout the pandemic, and even after the first original research on RTS, it ranged from up to four weeks[19] (2020) to three days after positive test (if asymptomatic)[26] or symptom resolution[28] (2022), 2) RTS screening protocols initially included mandatory evaluation of the cardiac systems, mostly for mild to severe disease,[9-12 19 22 24 25] but as time progressed, this approach was mostly replaced by symptom-guided testing, with the emphasis on cardiopulmonary symptoms.[20 21 23 26] A systematic review published in 2022[29] identified 17 studies with suggested RTT guidelines. These expert guidelines were evaluated mostly from a cardiologist perspective in 11 studies (65%) whilst six studies (35%) were opinions from sport physicians or orthopaedic surgeons. Increased physiological demands during exercise, and initial reports on the possible negative effects of either SARS-CoV-2 virus or treatment regimens on the athlete's heart,[30] might have caused more interest by cardiologists to assist with RTS guidance and hence the focus of screening protocols on the cardiac system. However, additional systematic reviews conducted during 2022, on acute/post-acute COVID-19 presentations and cardiac abnormalities, revealed the prevalence of cardiac-related complication to be relatively low in the athletic population (approximately 5%).[31 32] The American College of Sport Medicine recently suggested an approach to adapt pre-participation screening to include history on recent infectious disease (including SARS-CoV-2) with the focus on both the presence and severity of cardiovascular symptoms e.g. palpitation, chest pain/pressure or tightness and dyspnoea. Exertional cardiovascular symptoms, especially chest pain, should also be monitored in those athlete who has resumed training.[27] Chest pain and dyspnoea also warrants further investigations[2 3 7] and can also predict longer duration to RTT.[17 18]

The main findings of domain 3 of this literature were: 1) actual days to RTT were only reported in three studies (median of 17-30 days),[16-18] 2) duration of symptoms in four studies ranged from < 7 days[13] to a median of 10 days (IQR: 6-17),[17] 3) number of symptoms per athlete was reported in only one study (mean of 10.4 symptoms per athlete),[18] and 4) factors associated with prolonged RTT only in two studies. Chest pain,[17] and a symptom cluster of excessive fatigue, chills, fever, headache, altered/loss sense of smell, chest pain/pressure, difficulty in breathing and loss of appetite, were associated with prolonged RTT.[18] Symptoms

of the lower respiratory tract, have also been found to have a 2.1 time increased risk of time loss >28 days.[17]

The actual days to RTT is influenced by multiple factors. It could be determined by the clinical presentation and severity of SARS-CoV-2, or be influenced by the recommendation for the time (days) before training could resume. Certain symptoms may also warrant further investigation, as per screening protocol, thus delaying time to RTT.

Symptom duration in itself, is not an accurate indicator of time to RTT. However, the duration of symptoms, and the number of symptoms (as a possible indicator of infection severity) can have an influence on an athlete's ability to resume exercise or progressive increase training load to reach pre-infection level of sports performance i.e. return to full performance. Other factors associated with time to RTT and RTFP are limited.

3.5 KNOWLEDGE GAPS

Original data on actual days to RTS in athletes after SARS-CoV-2 are underreported and data on symptom characteristics (number and duration) are few. Symptoms do however appear to play an important role, not only in the screening of athletes, but also for predicting time course (days) to RTT. There are no data on the duration (days) to return to full performance (RTFP) or factors associated with prolonged RTFP.

3.6 CONCLUSION

During the course of the pandemic, there was a vast number of opinions on the recommended time course (days) before an athlete can resume training after a recent SARS-CoV-2 infection and specific screening protocols that should be conducted. Standard screening regimes were gradually replaced by individualised approaches, with the focus on demographics and co-morbidities,[33] abnormal clinical findings[20 23] or symptoms of concern.[26-28] It thus gradually evolved from a disease-orientated approach to a more customized, symptom-orientated approach.[34]

Despite the vast literature on expert opinion and reviews, the lack of original research remains. Specifically, research should be conducted on the screening of organ system involvement other than the cardiovascular system, symptoms characteristics (type and number of symptoms during the acute phase of infection) and other factors that may influence

time to RTT and RTFP. This knowledge will assist the SEM with scientific and safe RTS guidelines.

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The systematic review with meta-analysis in Chapter 2, and the narrative literature review in Chapter 3, identified knowledge gaps on the RTS parameters after a SARS-CoV-2 infection or other ARinf in the athletic population. However, to determine the extent of the health problem, and the subsequent impact it may have on RTS, the incidence of ARinf, including SARS-CoV-2 should first be determined.

Chapter 4 is the first original research article in this PhD thesis, determining the incidence of SARS-CoV-2 and other ARinf in a cohort of student rugby players over a 13-month study period.

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CHAPTER 4: Manuscript information

Title of manuscript

Incidence of respiratory infections (including SARS-CoV-2) is higher during contact training and competition compared to non-contact phases in a cohort of student rugby players – AWARE V

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CHAPTER 4: CONFERENCE PRESENTATION

Title

Incidence and risk factors associated with SARS-CoV-2 infections in Varsity Rugby Players

Conference

International festival of sports, exercise and medicine conference (IFSEMC)

Location

Pretoria, South Africa

Date

30 September 2022

Type of presentation

Platform

CHAPTER 4

Incidence of respiratory infections (including SARS-CoV-2) is higher during contact training and competition compared to non-contact phases in a cohort of student rugby players – AWARE V

4.1 ABSTRACT

Background

The incidence of acute respiratory infections (ARinf), including SARS-CoV-2 infection, in student rugby players during different phases from complete lockdown to competition is not known. Data on factors associated with incidence of these infections are limited.

Hypothesis

The incidence of ARinf/SARS-CoV-2 will be higher in phases of contact between players.

Study design

Retrospective cohort study

Level of evidence

Level 3

Methods

319 Top tier rugby players from 17 universities completed an online questionnaire. ARinf was reported during 4 phases over 14 months: phase 1 (individual training), phase 2 (non-contact team training), phase 3 (contact team training) and phase 4 (competition). Incidence (per 1000 player days) for 'All ARinf', and subgroups (SARS-CoV-2; 'Other ARinf') are reported. Symptom characteristics (type, duration and severity) and selected factors associated with ARinf were explored

Results

The incidence of 'All ARinf' (0.31) was significantly higher for SARS-CoV-2 (0.23) vs. 'Other ARinf' (0.08) ($p<0.01$) per 1000 player days. The incidence of 'All ARinf' ($p<0.01$) and SARS-CoV-2 ($p<0.01$) infection was significantly higher during contact (phases 3+4)

compared with non-contact (phases 1+2). Symptom characteristics were similar in subgroups. Demographics, level of sport, co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits were not associated with the incidence of ARinf.

Conclusions

In student rugby, contact training and competition are associated with a higher incidence of ARinf (including SARS-CoV-2). No associated factors could be identified.

Clinical relevance

Risk mitigation should be adapted in periods of contact training and competition in order to limit infections.

Keywords

COVID-19, athletes, risk, illness, epidemiology

4.2 INTRODUCTION

In most countries, including South Africa, sports were suspended in the early phases of the COVID-19 pandemic, with a gradual return to training and competition over months as public health and specific sporting code regulations changed. With the re-opening of team sport, the impact of re-introducing training or competitions on the spread of SARS-CoV-2 among players was unclear.

A consensus statement by the International Olympic Consensus group[1] on the reporting of injuries and illnesses in athletes, suggested the number of illnesses to be reported as incidence per 1000 player days, in order to compare studies regardless of study periods.

The incidence of SARS-CoV-2 in athletic populations during the early period after sport commenced, has been investigated mostly in elite football[2-5] during specified times of tournaments and competitions[4] or during a football season.[2] Most of these studies were conducted under specified conditions, i.e. the team followed specific protocols to mitigate risks of infection,[5] specific testing regimes,[2 4 5] or during a period of preparing and competing in tournaments.[4 5] These studies reported the illnesses over specified time as a percentage. The difference in the study periods, makes true comparisons between data difficult.

Similar data in rugby are limited. In two studies, transmission of SARS-CoV-2 in professional rugby players during periods of return to training or competition following lockdown was reported.[6 7] However, the incidence of acute respiratory infections (ARinf), including SARS-CoV-2 infection, in student rugby players during various phases from complete lockdown to return to full competition is not known. Risk factors associated with ARinf in athletes have not been reported.

The primary aim of the study was to determine the incidence (per 1000 player days) of acute respiratory infection (ARinf), including SARS-CoV-2, in student rugby players as they returned to competitive sport following complete lockdown during the COVID-19 pandemic. Additional aims were to describe symptom characteristics (type, duration and severity) during acute respiratory infection, and to determine if selected factors (demographics, level of sport participation, history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits) were associated with ARinf, including SARS-CoV-2, in this cohort of rugby players.

4.3 METHODS

This study is part of the **A**thletes **W**ith **A**cute **R**espiratory Inf**E**ctions (AWARE) studies, a multi-centre research program conducted by the Sport, Exercise Medicine and Lifestyle Institute (SEMLI) at the University of Pretoria, South Africa, in collaboration with the Institute of Sport and Exercise Medicine (ISEM) at the University of Stellenbosch, and student rugby in South Africa (Varsity Cup and Varsity Shield). All players consented to the study and ethical clearance was obtained from the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria for the AWARE umbrella protocol (REC 409/2020) and this specific study (REC 751/2019).

Study design

This was a retrospective cohort study.

Participants

Participants were male student rugby players from top (first and second) tier University rugby teams competing in an annual tournament in South Africa (April and May 2021). Practice contact ('friendly') matches were played during March 2021. Managers of these rugby teams were contacted with study information. 17 Universities, and 319 out of 468 players,

consented to partake in the study. None of the participating players were vaccinated against COVID-19. The vaccine was distributed in a phased roll-out from February 2021, and due to the young age of this population, no player was eligible to receive this vaccine during the study period.

Study period and phases of return to competitive sport during the COVID-19 pandemic

The study period was from April 2020 to May 2021 (14 months). National lockdown measures (restrictions on social interactions, movement of people, trade etc.) commenced in South Africa on 26 March 2020. During the study period, COVID-19 restrictions varied, and rugby players had to comply with both public health restrictions placed by the national government, and restrictions directed by the national rugby governing body. There were four phases from the time of total lockdown restrictions, to return to full competitive sport during the 14-month period. Phases 1 and 2 were characterised by non-contact between players, while phases 3 and 4 allowed full physical contact between players in the team setting. Each team commenced phase 2, 3 and 4 at different time points during the study period, dependant on local university regulations and readiness to open the campuses for access. The 4 phases were as follows:

Phase 1: Individual training (IT): players were confined to their homes, thereafter, exercise outside their homes was permitted (April 2020 to October 2020)

Phase 2: Non-contact team training (NCT): characterised by a gradual decrease in restrictions with opening of university campuses and training facilities where players were allowed to train as a team. Team training included an initial mandatory non-contact training period of 4 weeks to mitigate risk of injury (November 2020 to February 2021)

Phase 3: Contact team training (CT): contact training within individual teams was allowed (December 2020 to March 2021)

Phase 4: Competition (C): teams from different universities participated in full contact matches. This started with practice contact ('friendly matches') in March 2021 followed by the tournaments during April and May 2021

Risk mitigation strategies by government and national sport federation during COVID-19 pandemic

During the COVID-19 pandemic, the South African Government implemented regulations for the public to prevent the spread of SARS-CoV-2. Sport federations had to comply with these rules but these were not always possible in the sports environment. For example, facial

mask wearing and social distancing were not practical during training and competition. Risk mitigation strategies implemented by national government and the sport federation were applicable throughout the study period and outlined in Table 1.

Table 1: Preventative measures from government and the sport federation to limit SARS-CoV-2

Preventative measures	Phase 1 April to Oct 2020	Phase 2 Nov 2020 to Feb 2021	Phase 3 Dec 2020 to March 2021	Phase 4 March to May 2021
National public health policy				
Mandatory mask wearing in public places	+	+	+	+
Mandatory social distancing	+	+	+	+
Hand sanitizer use	+	+	+	+
Curfews	+	+	+	+
Restriction on number of persons at gatherings	+	+	+	+
Spectators	-	-	-	-
Sport federations policy				
Mask wearing in public places and when not training/competing	+	+	+	+
Mask wearing during exercise	+	-	-	-
Hand sanitizer use	+	+	+	+
Sanitizing of sports equipment	+	+	+	+
Mandatory SARS-CoV-2 testing (from March 2021)	-	-	-	+

+Preventative measure was mostly implemented
-Preventative measure was not always implemented

The implementation of these mitigation strategies and ARinf testing regimes for each team, were not evaluated in this study.

Data collection

The main data collection tool consisted of two electronic questionnaires hosted on the Research Electronic Data Capture (REDCap) platform.[8 9] Both questionnaires were distributed to the players at the beginning of the tournaments. The first questionnaire

contained sections on demographics (age, height and weight), level of sport participation (professional or amateur), history of any co-morbidities (cardiovascular, respiratory, gastrointestinal, central nervous system, metabolic, immune/blood disorders, renal or cancer), allergies, vaccination (influenza), injuries (acute and chronic) and lifestyle habits (smoking and alcohol consumption). The second questionnaire required the participant to indicate if: 1) *"they experienced symptoms of an acute respiratory infection, including SARS-CoV-2",* or 2) *"had current symptoms of acute respiratory infection, or SARS-CoV-2",* or 3) *"had no symptoms but tested positive for SARS-CoV-2"* or 4) *"had no symptoms of acute respiratory infection,"* in the past 12 months. Players reporting current acute symptoms (n=3) were excluded from the analysis. Participants were included if: 1) they reported no symptoms of ARinf, 2) they had symptoms of ARinf (with/or without confirmation of causative pathogen), 3) symptoms of SARS-CoV-2, 4) or asymptomatic with confirmed SARS-CoV-2 in the past 12 months.

Sub-groups of acute respiratory infections

For the analysis, players were divided into three subgroups based on their response to the questions on ARinf in the past 12 months: 1) Control subgroup (players reported no symptoms or diagnosis of ARinf/SARS-CoV-2), 2) SARS-CoV-2 subgroup [infection confirmed by polymerase chain reaction (PCR) or antigen testing], including asymptomatic players and 3) 'Other ARinf' subgroup (symptoms of ARinf but pathogen was not identified). Subgroups for 'Other ARinf' and SARS-CoV-2 were combined to form an 'All ARinf' group. The causative pathogen was not investigated in all the infections and therefore the 'Other ARinf' group may contain players with undiagnosed SARS-CoV-2.

Symptom characteristics and factors associated with ARinf

Data on symptom characteristics and factors associated with ARinf were collected using questionnaires 1 and 2 described above. These questionnaires have been described previously in detail.[10] There were 26 symptoms, listed according to anatomical regions "nose and throat", "chest and neck" or "whole body" (systemic). Participants with symptoms of ARinf/SARS-CoV-2 reported the type, duration (days) and severity (mild or moderate/severe) of symptoms during the acute phase of the infection.

Calculation of player days in each team during the four phases of the study

The team managers of each participating team provided the details for the exposure of their team members during each phase of the study. Managers provided the dates when their team commenced non-contact and contact training and when matches between teams started. Player days (exposure of players) were calculated for each team during each phase according to provided dates, and therefore player exposure for each phase varied between teams. Players completed the questionnaire at varying times during the competition and player days were calculated accordingly. Player days were therefore calculated on team level (as a cluster) for phases 1, 2 and 3, and then on an individual player basis for phase 4 (Supplementary Table A).

Testing regimes for SARS-CoV-2 differed among the teams in the months before the tournament commenced. However, for four weeks leading up to the tournament, every team had mandatory weekly testing. Players were also tested 48 to 72 hours before entering the competition environment ('bio-bubble'). During the tournament, players were only tested (SARS-CoV-2 antigen testing), if they had symptoms of ARinf.

Measures of outcome

The first outcome was to determine the incidence (per 1000 player days) of ARinf, including SARS-CoV-2, in the cohort for both the overall 14-month study period (120 177 player days), and for the four specific phases: (IT=85 734 player days; NCT=8 782 player days, CT=19 738 player days and C=5 923 player days) in the months preceding and including the tournament. Additional outcomes were: 1) to determine the period prevalence (%) of ARinf for the entire study period, 2) to describe the symptom characteristics (number, duration and severity) in rugby players with ARinf (including SARS-CoV-2), and 2) to determine if selected factors (demographics, level of sport participation, history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits) were associated with ARinf, including SARS-CoV-2, in this cohort of rugby players.

Statistical analysis

For this retrospective cohort study, demographic data, respiratory health data and illness data from the online surveys were exported from REDCap and then analysed in SAS (SASv9.4). The demographic data of the study population were described for the Control group (no infections), SARS-CoV-2 positive players and players with 'Other ARinf'. All demographic

related results were reported as mean (standard deviation), type of symptoms as percentage (95%CI), duration of symptoms as median (1st quartile; 3rd quartile) and severity of symptoms as percentage. For continuous outcomes comparing two groups a T-test (Satterthwaite or Pooled) was used for parametric data, and the Wilcoxon 2-sample Test for non-parametric data. Categorical outcomes were compared using both the Chisquare Test and Fisher's Exact Test. All incidences (per 1000 player days) and incidence comparisons were modelled with a generalized linear model with a Poisson distribution and a log link function. All comparisons within the SARS-CoV-2 and within the 'All ARinf' groups were modelled on team level with each team as a separate cluster, and an Exchangeable correlation structure. The one comparison within the 'Other ARinf' group could not be modelled on team level as there were too few other infections. For all tests, statistical significance was at 5%.

4.4 RESULTS

There were 319 consenting players in the study population. The demographics, level of sport participation, history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits for all participants and subgroups (Control, 'All ARinf', SARS-CoV-2 and 'Other ARinf') are reported in Table 2.

Table 2: Demographics, level of sport participation, history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits for all participants and subgroups (Control, All ARinf, SARS-CoV-2 and Other ARinf)

Variables	All participants (n=319)	Control n=282	All ARinf and subgroups		
			All ARinf n=37	SARS-CoV-2 n=28	Other ARinf n=9
Demographics					
Age (years) (mean) (SD)	22.0 (2.1)	22.1 (2.1)	21.8 (1.5)	21.9 (1.5)	21.4 (1.6)
BMI (mean) (SD)	28.6 (4.0) [a]	28.7 (4.0) [a]	28.1 (3.9)	27.4 (3.2)	30.2 (5.2)
Level of sport participation					
Professional n (%)	165 (52)	149 (53.0)	16 (43.2)	12 (42.9)	4 (44.4)
Amateur n (%)	153 (48)	132 (47.0)	21 (56.8)	16 (57.1)	5 (55.7)
History					
Co-morbidities (any) n (%)	56 (17.6)	47 (16.7)	9 (24.3)	8 (28.6)	1 (11.1)
Allergies n (%)	19 (6.0)	17 (6.0)	2 (5.4)	2 (7.1)	0
Influenza vaccination n (%)	65 (20.4)	56 (19.9)	9 (24.3)	8 (28.6)	1 (11.1)
Injuries (acute and chronic) in past 12 months n (%)[b]	82 (30.8) [b]	68 (28.9) [c]	14 (45.2) [d]	10 (40.0) [e]	4 (66.7) [e]
Lifestyle habits					
Alcohol consumption (yes) n (%)	168 (62.9) [f]	148 (62.7) [g]	20 (64.5) [d]	17 (68.0) [e]	3 (50.0) [e]
Smoking history (current/previous) (yes) n (%)	53 (19.9) [f]	46 (19.5) [g]	7 (22.6) [d]	6 (24.0) [e]	1 (16.7) [e]

% has been adjusted for missing values in denominator
BMI, body mass index; ARinf, acute respiratory infection
Number of missing participants: a=5 b=53, c=47, d=6, e=3, f=52, g=46

The mean (SD) age of the participants was 22 (2.1) years, and the majority (52%) were professional players. History of any co-morbidity was reported by 18% of participants.

Incidence of ARinf for the study period

During the 14-month study period, the total number of player days were 120 177. The incidence per 1000 player days of 'All ARinf' was 0.31 (95%CI: 0.21-0.41). The incidence of SARS-CoV-2 infection was 0.23 (95%CI: 0.15-0.32) and this was significantly higher than 'Other ARinf' 0.08 (95%CI: 0.03-0.12) ($p<0.01$).

The period prevalence during the 14-month study period was 11.6% (n=37) for 'All ARinf', 8.8% (n=28) for SARS-CoV-2 and 2.8% (n=9) for 'Other ARinf'.

Incidence of ARinf during the four phases of return to competitive sport following complete lockdown during the COVID-19 pandemic

The player days and the incidence per 1000 player days of 'All ARinf' (n=37), SARS-CoV-2 (n=28) and 'Other ARinf' (n=9) in the four different phases of return to competitive sport are depicted in Table 3. Phases 1 and 2 were characterised by non-contact between players and phases 3 and 4 by physical contact between players.

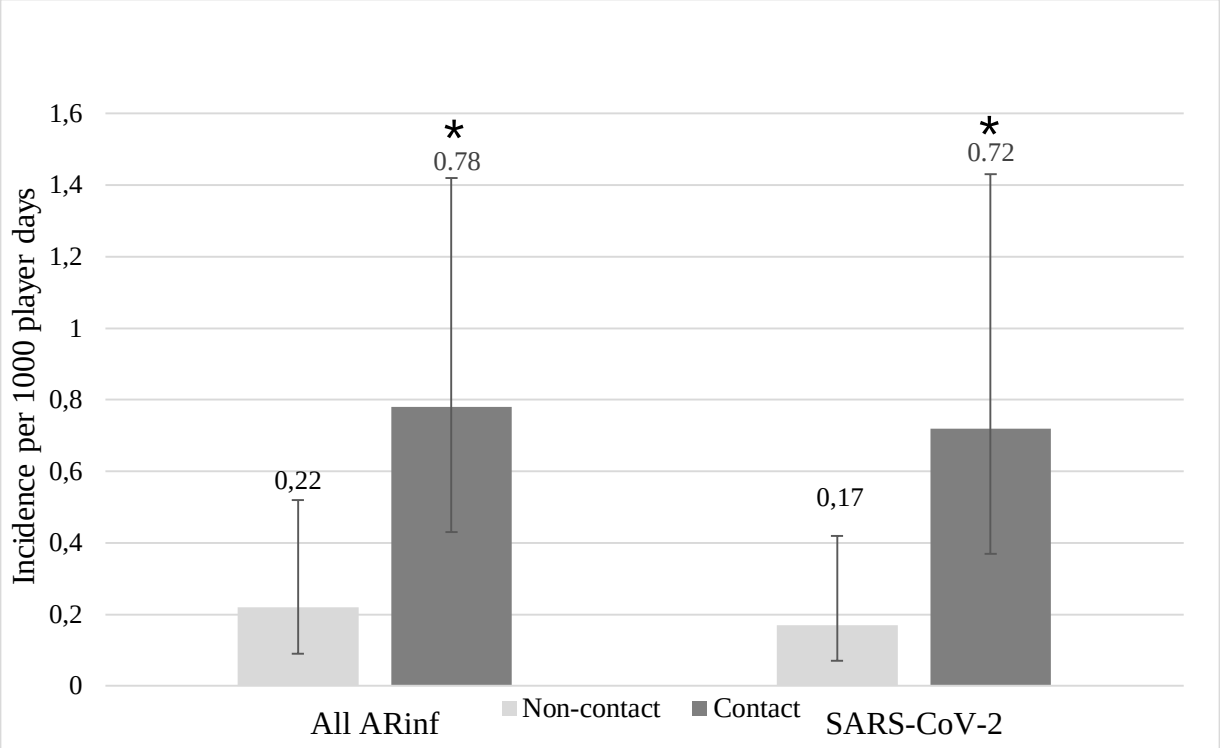
Table 3: Incidence per 1000 player days of All ARinf, SARS-CoV-2 and Other ARinf in the four different phases of return to competitive sport following complete lockdown during the COVID-19 pandemic

Phases	Player days	Incidence per 1000 player days (95% CI)		
		All ARinf (n=35)	SARS-CoV-2 (n=28)	Other ARinf # (n=7)
Non-contact	94 516	0.22 (0.09-0.52)	0.17 (0.07-0.42)	-
Phase 1: Individual training (IT)	85 734	0.15 (0.07-0.31)	0.09 (0.04-0.22)	0.06 (0.02-0.14)
Phase 2: Non-contact team training (NCT)	8 782	0.31 (0.07-1.36)	0.32 (0.07-1.36)	-
Contact	25 661	0.78 (0.43-1.42) **	0.72 (0.37-1.43) **	-
Phase 3: Contact team training (CT)	19 738	0.56 (0.27-1.17) *	0.47 (0.20-1.11) *	0.10 (0.03-0.41)
Phase 4: Competition (C)	5 923	1.10 (0.49-2.43) *	1.11 (0.49-2.53) *	-

#Two participants did not indicate date of infection in the 'Other ARinf' subgroup and analysis on team cluster level could not be performed due to few number of infections
**p<0.05 contact vs. non-contact
*p<0.05 compared to phase 1
ARinf, acute respiratory infection

The main observation was that the incidence of 'All ARinf' and SARS-CoV-2 progressively increased from phases 1 to 4. The incidence of 'All ARinf' [IR 3.7 (95%CI: 1.4-9.9)] and SARS-CoV-2 infection [IR 5.0 (95%CI: 1.4-17.6)] was significantly higher in phases 3 compared with phase 1 (both p=0.01). There was also significant difference in comparing phase 4 and phase 1 for 'All ARinf' [IR 7.2 (95%CI: 3.8-14.0 (p<0.01)] and SARS-CoV-2 [IR 11.7 (95%CI: 5.0-27.6) (p<0.01)].

The incidence of 'All ARinf' [IR 3.6 (95%CI: 1.4-9.1)] and SARS-CoV-2 [IR 4.2 (95%CI: 1.6-11.2)] during contact (phase 3+4) were also significantly higher compared to non-contact (phase 1+2) (both p<0.01) (Figure 1).



* p<0.05 contact vs non-contact
ARinf, acute respiratory infection

Figure 1: The incidence per 1000 player days of All ARinf and SARS-CoV-2 during non-contact and contact phases

Symptom characteristics of ARinf in rugby players

The total number of symptoms during the acute phase for 'All ARinf', SARS-CoV-2 and 'Other ARinf' per anatomical region are listed in Table 4. In the SARS-CoV-2 subgroup, 4 players were asymptomatic and omitted from these results.

Table 4: The total number of symptoms (mean, 95%CI) during the acute phase of respiratory infections per anatomical region for All ARinf, SARS-CoV-2 and Other ARinf

Symptoms	All ARinf n=33	SARS-CoV-2 n=24 #	Other ARinf n=9	p-value
Nose and throat	2.2 (1.7-2.7)	2.1 (1.6-2.7)	2.4 (1.4-3.5)	0.649
Chest and neck	1.1 (0.6-1.5)	1.2 (0.7-1.8)	0.8 (0-1.7)	0.314
Whole body	1.2 (0.6-1.7)	1.2 (0.7-1.6)	1.2 (0-3.1)	0.225
All symptoms	4.5 (3.4-5.6)	4.5 (3.3-5.7)	4.4 (1.6-7.3)	0.683

Asymptomatic SARS-CoV-2 excluded (n=4)
ARinf, acute respiratory infection

The mean total number of all symptoms (number: 95%CI) in the 'All ARinf', SARS-CoV-2 and 'Other ARinf' infection groups were 4.5 (3.4-5.6), 4.5 (3.3-5.7) and 4.4 (1.6-7.3)

respectively. The mean total number of all symptoms and symptoms by main anatomical region were not significantly different between the subgroups.

The duration of symptoms (days) during the acute phase of respiratory infections for all subgroups per anatomical region is reported in Supplementary Table B. There was no significant difference in duration between the 'Other ARinf' and SARS-CoV-2 subgroups of infection for the different anatomical regions: "nose and throat" (p=0.59), "chest and neck" (p=0.31) or "whole body" symptoms (p=0.17).

The severity of symptoms during the acute phase of respiratory infections for 'All ARinf', SARS-CoV-2 and 'Other ARinf' are reported in Supplementary Table C. Most symptoms in the "nose and throat" region were reported as more severe in the SARS-CoV-2 subgroup, compared to the 'Other ARinf' subgroup.

Factors associated with acute respiratory infections

Factors (demographics, level of sport participation, history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits) associated with ARinf are reported in Table 5.

Table 5: Demographics, level of sport participation, history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits as possible factors associated with acute respiratory infection

Variable	Control n=282	All ARinf n=37	p-value *	SARS-CoV-2 n=28	p-value **
Demographics					
Age (years) (mean) (SD)	22.1 (2.1)	21.8 (1.5)	0.402	21.9 (1.5)	0.706
BMI (mean) (SD)	28.7 (4.0) [a]	28.1 (3.9)	0.430	27.4 (3.2)	0.116
Level of sport participation					
Professional (vs amateur) n (%)	149 (53.0) [b]	16 (42.9)	0.263	12 (42.9)	0.304
History					
Any co-morbidity (yes) n (%)	47 (16.7)	9 (24.3)	0.250	8 (28.6)	0.123
Allergies (yes) n (%)	17 (6.0)	2 (5.4)	1.000	2 (7.1)	0.685
Influenza vaccination (yes) n (%)	56 (19.9)	9 (24.3)	0.526	8 (28.6)	0.277
Injuries (acute/chronic) in past 12 months (yes) n (%)	68 (28.9) [c]	14 (45.2) [d]	0.066	10 (40.0) [e]	0.251
Lifestyle habits					
Alcohol consumption (yes) n (%)	148 (62.7) [f]	20 (64.5) [d]	0.845	17 (68.0) [e]	0.602
Smoking history (current/previous) (yes) n (%)	46 (19.5) [f]	7 (22.6) [d]	0.685	6 (24.0) [e]	0.601

* Difference between Control and 'All ARinf' subgroups
** Difference between Control and SARS-CoV-2 subgroups
Other ARinf group was too small to compare to Control
% has been adjusted for missing values in denominator
BMI, body mass index; ARinf, acute respiratory infection
Number of missing participants: a=5, b=1, c=47, d=6, e=3, f=4

There was no significant difference between either the Control vs. 'All ARinf' or the Control vs. SARS-CoV-2 for any of the selected factors including: demographics, level of sport participation, history of any co-morbidities, allergies, influenza vaccination, acute or chronic injuries and lifestyle habits ($p>0.05$).

4.5 DISCUSSION

The main findings of this study were: 1) the incidence of 'All ARinf' in a cohort of student rugby players over a 14-month period during the COVID-19 pandemic, was 0.31 per 1000 player days with a period prevalence of 11.6%; 2) the incidence of SARS-CoV-2 infection (0.23) was significantly higher than 'Other ARinf (0.08); 3) the incidence of 'All ARinf' and SARS-CoV-2 infection progressively increased during the four different phases of return to competitive sport following lockdown, with a significantly higher incidence during contact phases compared with non-contact phases; 4) symptoms during the acute phase did not differ significantly in the subgroups; and 5) factors (demographics, level of sport participation,

history of co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits) were not associated with the incidence of ARinf/SARS-CoV-2.

To date, most studies reported only the period prevalence of SARS-CoV-2 infection. In early studies on professional European football players resuming sport during the COVID-19 pandemic, the period prevalence of SARS-CoV-2 infection (over 9-11 weeks) varied between 0.5 and 2.7%.[3-5] In a study among Brazilian football teams over a 6-month period, weekly PCR testing showed that 11.7% of players tested positive for SARS-CoV-2.[2] In another cohort study among college football players over 3-month period, the period prevalence of SARS-CoV-2 was 11.6%.[11] Our period prevalence of 'All ARinf' was 11.6% and for SARS-CoV-2 infection was 8.8%, but this cannot strictly be compared to the prevalence in the mentioned studies due to differences in the study periods in published studies (2-6 months vs. 14 months). However, the period prevalence of SARS-CoV-2 infection during the match phase (4.4%) in one study, was higher compared to entering (1.6%) and exiting (1.2%) periods of quarantine before and after matches.[5] This supports our finding that the risk of infection is higher during competition. Studies also differed considerably in the frequency of SARS-CoV-2 testing (varying from 3/week to weekly). Testing in our population differed for teams during the preparation period, but testing was mandatory in the 4 weeks prior to the tournament, 48-72 hours before entering the tournament environment and when a player was symptomatic during the competition phase.

We suggest that reporting the incidence of ARinf per 1000 player days is more appropriate to make comparisons between studies, irrespective of study periods. In a systematic review and meta-analysis for multi-coded sports, the incidence per 1000 player days of ARinf (suspected/confirmed) was 4.9 during tournaments.[12] Our incidence of 'All ARinf' (0.31) is considerably lower than that reported in this review, that was conducted before the COVID-19 pandemic. The lower incidence of ARinf in our study is likely due to the risk mitigation strategies throughout our study period. Although these strategies were implemented (Table 1), they were not always practical in the contact sport setting.

To date, the incidence of SARS-CoV-2 in rugby was only reported in one study over a 6-month period in South African elite rugby players.[7] In this study, the overall incidence (per 1000 player days) of SARS-CoV-2 was 1.23, and this is higher than our overall incidence. A fundamental difference between our study and this study, was that players were tested for SARS-CoV-2 on a weekly basis and therefore included asymptomatic players. This study also reported the incidence of SARS-CoV-2 was higher during contact training 1.04 (95%CI:

0.36-1.71) and competition 1.54 (95%CI: 1.00-2.10) compared to non-contact training (nil infections). This finding correlates with our data showing an increasing incidence of SARS-CoV-2 infection during contact team training (0.47) and competition (1.11).

Compared to a study with similar reporting on SARS-CoV-2 symptoms characteristics,[5] our participants had more "chest and neck" and "whole body" symptoms. Apart from a longer duration of loss/altered sense of smell, chest pain, and shortness of breath, the duration of other symptoms had a similar mean duration of <7 days. This finding correlates with the data reported in a published systematic review on ARinf (before the COVID-19 pandemic) in athletes, where the mean symptom duration of ARinf was 7.1 days.[13]

In our study, factors including demographics, history of any co-morbidities, allergies, influenza vaccination, injuries, or lifestyle habits were not associated with the incidence of ARinf. At the time of the study, SARS-CoV-2 infections were predominantly of the Ancestral virus and Beta variant and our study population was unvaccinated for COVID-19. However, in a study on 414 athletes[14] competing in mixed sport and with a SARS-CoV-2 prevalence of 8.5%, age (under 27 years old), smoking history and a team mate with a positive COVID-19 test, were factors associated with potential risk of SARS-CoV-2.

Our study was conducted on a defined cohort of players over a 14-month period, and we compared the incidence of ARinf during different phases of return to competitive sport during the COVID-19 pandemic.

The following limitations of the study are acknowledged. We collected self-reported data from players using questionnaires and this could introduce recall bias. Data were collected and analysed per team, and not for individual players. There was no regular SARS-CoV-2 PCR/antigen testing throughout the study period. Players could only report SARS-CoV-2 infection if the diagnosis was confirmed. However, pathogens for 'Other ARinf' were not identified. Infections during the competition phase, might be underreported as players completed the questionnaire during varying times during the tournament. Exposure days for each player in the competition phase were calculated up to the date of the completion of individual questionnaires. Infections after the completion of the questionnaire were not included.

We included a large number of players in our cohort but the number of ARinf was small, particularly the 'Other ARinf' subgroup. Comparisons between subgroups could therefore not be done for all variables. Furthermore, it is possible that symptomatic players in the 'Other

ARinf' group may not have been tested for SARS-CoV-2 or had a false negative test. The national public health risk mitigation measures were the same throughout the study period, but individual compliance to these measures could not be determined.

4.6 CONCLUSION

The incidence of ARinf (including SARS-CoV-2) in a cohort of student rugby players increased progressively during 4 phases from lockdown to full competition. A key finding was that the incidence was higher during contact phases compared to non-contact phases despite similar public health risk mitigation measures for all phases. No demographic factors, level of sport participation or history of co-morbidities and lifestyle habits were associated with the incidence of ARinf in this cohort.

Clinical recommendations

Contact training is crucial in contact sports such as student rugby to prepare for tournaments and competition. Due to the higher incidence of ARinf during this period, sport and exercise clinicians should assist with strategies to decrease risk of transmission, early identification of infection, isolation of players, appropriate clinical assessment, and safe return to training (RTT) guidance after infection. This study has a strength of recommendation C.[15]

Supplementary material

Supplementary Table A: Calculation of player days for each team during the four different phases for All ARinf (acute respiratory infection)
Supplementary Table B: Duration of specific symptoms during the acute phase of respiratory infections for All ARinf (acute respiratory infection), SARS-CoV-2 and Other ARinf
Supplementary Table C: Severity of specific symptoms during the acute phase of respiratory infections for All ARinf (acute respiratory infection), SARS-CoV-2 and Other ARinf

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Disclosure statement

The authors report that there are no competing interests to declare.

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Data availability

The authors confirm that the findings of this study are supported by data available within this article.

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In Chapter 4, the incidence of SARS-CoV-2 has been described in a cohort of student rugby players. After a time-loss respiratory infection, including SARS-CoV-2, the duration (days) to return to training (RTT), is the first important clinical decision in the return to sport (RTS) continuum.

The time line to RTT, and factors associated with prolonged RTT, have been identified as a knowledge gap in the narrative literature review (Chapter 3).

Chapter 5 is an original research article exploring the time to RTT in a cohort of athletes, and explore if there are factors associated with prolonged RTT.

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Chapter 5: Publication information

Title of publication

Symptom number and reduced pre-infection training predict prolonged return to training after SARS-CoV-2 in athletes: AWARE IV

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CHAPTER 5: CONFERENCE PRESENTATION

Title

Symptom number and reduced pre-infection training predict prolonged return to training after SARS-CoV-2 in athletes: AWARE IV

Conference

Early Career Scientist Convention (ECSC)

Location

Cape Town, South Africa

Date

25 October 2022

Type of presentation

Platform

CHAPTER 5

Symptom number and reduced pre-infection training predict prolonged return to training after SARS-CoV-2 in athletes: AWARE IV

5.1 ABSTRACT

Purpose

To determine factors predictive of prolonged return to training (RTT) in athletes with recent SARS-CoV-2 infection.

Methods

Cross-sectional descriptive study. Athletes not vaccinated against COVID-19 (n=207) with confirmed SARS-CoV-2 infection (predominantly ancestral virus and beta-variant) completed an online survey detailing the following factors: demographics (age, sex), level of sport participation, type of sport, co-morbidity history and pre-infection training (training hours 7 days pre-infection), SARS-CoV-2 symptoms (26 in three categories; "nose and throat", "chest and neck", and "whole body") and days to RTT. Main outcomes were hazard ratios (HR; 95%CI) for athletes with vs. without a factor, explored in univariate and multiple models. HR<1 was predictive of prolonged RTT (reduced % chance of RTT after symptom onset). Significance was $p<0.05$.

Results

Age, level of sport participation, type of sport and history of co-morbidities were not predictors of prolonged RTT. Significant predictors of prolonged RTT (univariate model) were (HR;95%CI): female (0.6;0.4-0.9; p=0.01), reduced training in the 7 days pre-infection (1.03;1.01-1.06; p=0.003), presence of symptoms by anatomical region [any "chest and neck" (0.6; 0.4-0.8; p=0.004) and any "whole body" (0.6; 0.4-0.9; p=0.025)], and several specific symptoms. Multiple models show that the greater number of symptoms in each anatomical region (adjusted for training hours in the 7 days pre-infection) was associated with prolonged RTT ($p<0.05$).

Conclusion

Reduced pre-infection training hours and the number of acute infection symptoms may predict prolonged RTT in athletes with recent SARS-CoV-2. These data can assist physicians as well as athletes/coaches in planning and guiding RTT. Future studies can explore whether these variables can be used to predict time to return to full performance and classify severity of other acute respiratory infection in athletes.

Keywords

Predictors, COVID-19, return-to-sport, respiratory tract infections

5.2 INTRODUCTION

An acute respiratory tract infection is the most common cause of acute illness in athletes and accounts for approximately 50% of illness episodes during tournaments or competitions.[1-3] The outbreak of the COVID-19 pandemic increased this burden of respiratory disease in the general population and in athletes. In athletes with acute respiratory infection, an important clinical decision is whether an athlete, who discontinued training for a period during the infection, can return to training or sport.

The term “return to sport” (RTS) following injury in athletes is well-established, although the definition varies.[4] However, similar studies on RTS after illness are lacking. Historically, RTS was considered as a single end-point when the athletes “return to competition or game”, but it is now recognised that RTS is a continuum[5] starting from returning to participation (training) and is completed on return to previous levels of performance. The Sport and Exercise Medicine (SEM) clinician is faced with two important clinical decisions along this continuum. The first clinical decision is related to the resumption of training following illness, and the measurable variable is the time (days) before an athlete starts training again following an infection, defined as days to “return to training” (RTT). Once an athlete starts training following an acute illness, the progression of training load is usually gradual. A second clinical decision is to determine when the athlete in training can return to previous levels of competitive sport and full performance. Full RTS is the end point of this continuum. Data on RTS in athletes following SARS-CoV-2 infection, and studies on factors influencing decisions on the time course for RTT and the return to full performance, are limited.[6] To date, most RTS guidelines following SARS-CoV-2 infection in athletes are based on expert

opinion, with the majority of studies focused on the cardiovascular system.[7 8] In the general population, symptom clusters are predictive of short- and long-term clinical outcomes of SARS-CoV-2 infection.[9 10] Demographics, level of sport participation, type of sport, co-morbidities, pre-infection training and acute symptoms characteristics, are factors that may determine RTT after SARS-CoV-2 infection, but these have not been explored.

The main aim of this study was to determine if selected factors are predictive of prolonged RTT in athletes with recent SARS-CoV-2 infection. Factors that were explored include demographics (age, sex), level of sport participation, type of sport, history of co-morbidities, pre-infection training (7 days before onset of infection) and symptom characteristics of the acute infection (by specific symptoms, anatomical region, and number of symptoms). Physicians responsible for athlete medical care are faced with the challenge of providing guidance in the process of RTS after acute respiratory infection. These data could be used to guide RTT clinical decision-making in athletes with a recent SARS-CoV-2 infection.

5.3 METHODS

Study Design and Setting

The **A**thletes **W**ith **A**cute **R**espiratory Inf**E**ctions (AWARE studies) is a multi-centre study, led by the Sport, Exercise Medicine and Lifestyle Institute (SEMLI) at the University of Pretoria in South Africa, together with researchers from a number of academic institutions, sports federations and some members of a subgroup of the International Olympic Committee (IOC) Consensus group on "Acute Respiratory Illness in the Athlete". This is a descriptive cross-sectional study using data collected between 20 July 2020 and 20 May 2021 during the first (ancestral virus) and second waves (predominantly beta-variant) of SARS-CoV-2 infection. During this study period competitive sport was limited due to the COVID-19 restrictions and only gradually re-introduced, initially for professional athletes, and later in recreational settings. At the start of the study, COVID-19 vaccines were not available. In 2021, the COVID-19 vaccination became available in a phased roll out, initially only for higher risk and older individuals. Thus, at the time of closure for participant inclusion for this study (May 2021), no participants were vaccinated. Ethical clearance was obtained from the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria (REC 409/2020).

Participants, Survey Instrument and Data Collection

Athletes are defined as "competing at varying levels in any sport, training for a minimum of 3 hours per week" and were recruited using social media platforms, existing databases and the SEMLI medical practice. Participants (n=207) were included if they were: 1) aged 18 to 60 years, 2) reported a SARS-CoV-2 infection, confirmed by positive Polymerase Chain Reaction (PCR) or antigen test in the past 6 months, 3) gave electronic informed consent on the online survey housed on the Research Electronic Data Capture (REDCap) platform[11 12] and 4) provided information on the number of days to RTT. Survey details have previously been described[6] and included questions on 1) demographics (age and sex), 2) level of sport participation (professional - elite level/full-time or amateur – part time/hobby), 3) type of sport (power, endurance, skilled or mixed)[13], 4) history of co-morbidities, 5) symptoms of acute SARS-CoV-2 infection (type, number, duration, and severity) per anatomical region ["nose and throat", "chest and neck" and "whole body"(systemic)], and 6) training history (hours of training 0 to 35 days before onset of infection). SARS-CoV-2 vaccines were not available at the time the study commenced and was not included in this questionnaire. Participants were requested to indicate if they 1) have started training again after recent infection (n=138), 2) have not started training (n=61), or 3) continued training throughout recent infection (n=8). For those who have started training, the days to return to the first training session were reported in response to the following question: "*How many days were there between the start of your symptoms and the return to your first training session*?"

Patient and Public Involvement (PPI)

PPI was considered for this study. Athletes who had experienced an acute respiratory infection (ARinf), including SARS-CoV-2, and medical practitioners that regularly treat athletes with acute respiratory tract infections, were asked to provide feedback on the questionnaire in the development stages.[6]

Measures of outcome

The primary outcome measure was the self-reported number of days to return to the first training session (RTT) after recent SARS-CoV-2 infection. Factors explored as possible predictors of RTT included, demographics (age, sex), level of sport participation, type of sport, history of co-morbidities in organ systems (respiratory, cardiovascular, gastrointestinal, nervous, metabolic, renal systems and cancer), training history in the 7 days before acute

infection, and symptoms of acute SARS-CoV-2 infection (by specific symptoms, anatomical region, and number of symptoms).

Statistical analysis of data

Demographics, level of sport participation, type of sport[13], history of co-morbidities and pre-infection training history in athletes were described using n (%) or mean (SD). The responses to the 26 types of SARS-CoV-2 symptoms (8 "nose and throat", 8 "chest and neck" and 10 "whole body") were described in three ways: 1) the presence of symptoms [number of athletes (n)(%; 95%CI)], 2) the duration in days (median: Q1-Q3) and 3) the severity [number (%) of mild and moderate or severe].

For the training resumption variable: 1) participants reporting RTT days (n=138), the actual days to RTT were recorded, 2) participants that did not start training (n=61), the days RTT with censoring were recorded, and 3) participants that continued training (n=8), 0 days RTT were recorded. For the days to RTT analysis, 207 participants were used for this analysis. For the Cox regression modelling of factors associated with a prolonged RTT the analysis was done in stages. For the univariate modelling, the independent factors explored were: 1) demographics, level of sport participation, type of sport, history of co-morbidities and pre-infection training history, 2) the presence of specific individual symptoms, 3) the presence of any symptoms by anatomical region, and 4) the number of symptoms by anatomical region. The individual symptoms were not considered in the multiple regression model, but instead the variables "presence" and "number" of symptoms by anatomical region were considered. Separate multiple regression models for "presence" and "number" of symptoms were conducted, adjusting for training hours in the 7 days before the onset of the infection. The Hazard Ratio (HR; 95%CI) was reported with Chi-Square (p-values) (type 3 test) for significance ($p<0.05$). Cox regression assumption of proportional hazards was checked. For these data, a $HR<1$ indicates a prolonged RTT after the onset of symptoms.

5.4 RESULTS

Demographics, level of sport participation, type of sport, history of co-morbidities and pre-infection training

The demographic variables, level of sport participation, type of sport, history of co-morbidities and pre-infection training in athletes with recent SARS-CoV-2 (n=207) are shown in Table 1.

Table 1: Demographics, level of sport participation, type of sport, history of co-morbidities and pre-infection training history in athletes with recent SARS-CoV-2 (n=207)

Variable	SARS-CoV-2 (n=207)
Demographics	
Age (mean, SD)	27.9 (9.9)
Male sex (n, %) [a]	121 (65.8)
Height (cm) (mean, SD) [b]	178.3 (13.3)
Body weight (kg) (mean, SD) [a]	80.2 (19.1)
Level of sport participation	
Professional sports (n, %) [a]	82 (44.6)
Years sporting experience (mean, SD) [b]	11.0 (7.4)
Type of sport [c]	
Power	10 (5.5)
Endurance	75 (41.4)
Mixed (including Skills n=3)	96 (53.0)
History of co-morbidities	
Number of co-morbidities per participant (mean, SD)	0.7 (1.1)
Any co-morbidity (yes) (n, %)	87 (42)
Respiratory	45 (22.7)
Cardiovascular risk factors	20 (9.7)
Gastrointestinal	32 (15.5)
Nervous system	22 (10.6)
Allergies (yes) (n,%)	36 (17.4)
Pre-infection training history	
Training 7 days prior to onset of symptoms (hrs/week) (mean, SD)	9.7 (6.9)
Weekly training 2-5 weeks prior to onset of symptoms (hrs/week) (mean, SD)	11.7 (7.6)

Number of participants with missing data: a=23, b=25, c=26

The mean age of the study population was 28 years, the majority were males (66%) and 45% were professional athletes. Participants mostly competed in mixed (53%) (including 3

athletes with skill sport) and endurance sports (41%). A history of any co-morbidity was reported by 42% of participants.

Symptoms (number, duration and severity) of SARS-CoV-2 infection in study participants

The mean number of SARS-CoV-2 symptoms (out of 26) in the acute infective phase was 7.3 per athlete (95%CI 6.7-7.9). The number (n; %; 95%CI), duration (days) and severity of symptoms by anatomical region and specific symptoms is shown in Supplemental Digital Content 1. The mean number of "nose and throat" symptoms was 2.8 (2.6-3.1), and "chest and neck" symptoms was 2.1 (1.9-2.4). 21 participants reported "other whole body" symptoms that were included in the questionnaire as "free text". The mean number of "whole body" (inclusive of "other whole body") symptoms was 2.3 (2.1-2.6). The four most common symptoms were "excessive fatigue" (58%), "headache" (57%), "altered/loss of sense of smell" (54%) and "blocked nose" (51%). Symptoms with the longest duration were "fast breathing/shortness of breath", "excessive fatigue", "loss of appetite", "red watery eyes" and "altered/loss of smell or taste" (all median of 7 days). The following symptoms were most commonly reported as moderate or severe: "excessive fatigue" (43%), "loss/altered sense of smell and taste" (42% and 36% respectively), "headache" (38%) and "muscle aches" (29%).

Days to RTT

The median days for RTT for the participants who had started training, was 14 days (interquartile range 10-21 days), with a minimum of 0 days (for those who continued training throughout the infection period) and the maximum duration to RTT was 87 days (for those who had not started training at the time of completing the questionnaire).

Factors associated with prolonged RTT following SARS-CoV-2 infection (univariate models)

Demographics, level of sport participation, type of sport, history of co-morbidities and pre-infection training history (univariate model)

The Hazard Ratio (HR and 95%CI) for demographics (age and sex), level of sport participation, type of sport, history of co-morbidities, and pre-illness training history is shown in Table 2. HR<1 indicates a lower chance of RTT (prolonged RTT) after the onset of the infection.

Table 2: Demographics, level of sport participation, type of sport, history of co-morbidities and pre-infection training history as possible factors associated with prolonged return to training (RTT) (n=207) (Univariate model)

Variable	Hazard ratio * 95%CI	Chi-Square	p-value
Demographics			
Age	0.99 (0.98-1.01)	1.09	0.297
Sex: Females (vs. Males)	0.6 (0.4-0.9)	6.66	**0.010**
Level of sport participation			
Professional sport (vs. recreational)	1.4 (1.0-2.0)	3.58	0.058
Type of sport			
Power (reference)	-		
Endurance	1.06 (0.51-2.19)	0.026	0.872
Mixed (including Skills)	0.94 (0.46-1.92)	0.032	0.857
History of co-morbidities			
Number of co-morbidities	0.9 (0.8-1.0)	2.05	0.152
Any co-morbidities by organ system (No vs. Yes) ^	0.8 (0.6-1.2)	0.959	0.328
Respiratory	1.0 (0.6-1.4)	0.054	0.816
Cardiovascular risk factors	0.8 (0.5-1.4)	0.528	0.467
Gastrointestinal	0.7 (0.5-1.1)	2.31	0.129
Nervous	0.8 (0.5-1.4)	0.764	0.382
Allergies	0.9 (0.6-1.3)	0.458	0.499
Pre-infection training history			
Training 7 days prior to onset of symptoms (hrs/week)	1.03 (1.01-1.06)	8.74	**0.003**
Weekly training 2-5 weeks prior to onset of symptoms (hrs/week)	1.10 (0.99-1.03)	1.05	0.307

* Ratio of the hazard of an individual with the presence of the co-variate compared to the hazard of RTT for an individual without the presence of the co-variate
^ Co-morbidities in other organ systems were too few for further analyses (this included participants with a history of cardiovascular disease)

Age, level of sport participation, type of sport and history of co-morbidities were not associated with a more prolonged RTT. In this univariate model, the following variables were significantly associated with a prolonged RTT: females (p=0.01) and reduced hours of training in the 7 days prior to infection (p=0.003).

The association between the presence of specific symptoms and prolonged RTT (univariate model)

The hazard ratio (HR) was derived as the ratio of the hazard of RTT for an individual with the symptom, compared to the hazard of RTT for an individual without the symptom. The Hazard Ratio (HR and 95%CI) for the presence of specific symptoms is shown in Table 3.

Table 3: The Hazard Ratio (95%CI) for the presence of specific symptoms in athletes and prolonged return to training (RTT) (n=207) (Univariate model)

Anatomical region	Symptom	n	Hazard Ratio (95% CI) *	Chi-Square	p-value
Nose and Throat	Sore/scratchy throat	102	1.0 (0.7-1.4)	0.03	0.863
	Hoarseness	26	0.6 (0.3-1.0)	4.09	**0.043**
	Blocked/plugged nose	105	0.9 (0.6-1.2)	0.72	0.397
	Runny nose	45	0.7 (0.5-1.1)	2.03	0.154
	Sinus pressure	65	0.7 (0.5-1.1)	2.73	0.098
	Sneezing	32	0.9 (0.5-1.4)	0.24	0.569
	Altered/loss sense of smell	111	0.7 (0.5-1.0)	3.41	0.065
	Altered/loss sense of taste	98	0.7 (0.5-1.0)	3.34	0.068
Chest and Neck	Dry cough	75	0.7 (0.5-1.0)	3.54	0.060
	Wet cough	47	1.1 (0.7-1.6)	0.06	0.813
	Difficulty in breathing	46	0.6 (0.4-1.0)	4.7	**0.030**
	Fast breathing/shortness of breath	46	0.7 (0.5-1.0)	3.22	0.073
	Chest pain/pressure	42	0.6 (0.4-1.0)	4.08	**0.044**
	Chest tightness	42	0.8 (0.5-1.2)	1.33	0.248
	Headache	118	0.9 (0.6-1.2)	0.49	0.480
	Red/watery/scratchy eyes	27	0.9 (0.5-1.4)	0.4	0.527
Whole Body	Fever	73	0.8 (0.5-1.1)	2.64	0.104
	Chills	43	0.5 (0.3-0.8)	7.24	**0.007**
	Excessive fatigue	119	0.7 (0.5-1.0)	4.95	**0.026**
	General muscle aches and pains	88	1.1 (0.8-1.5)	0.08	0.784
	Skin rash ^	6	-	-	-
	Abdominal pain	19	0.5 (0.2-0.9)	4.78	**0.029**
	Nausea	27	0.6 (0.4-1.1)	2.72	0.099
	Vomiting ^	1	-	-	-
	Diarrhoea	19	1.0 (0.6-1.7)	0.006	0.936
	Loss of appetite	63	0.6 (0.4-0.8)	9.31	**0.002**
	Other whole body symptoms	21	0.8 (0.5-1.3)	0.88	0.347

*HR is the ratio of the hazard of RTT for an individual with the symptom compared to the hazard of RTT for an individual without the symptom. A HR<1 indicates a lower chance of RTT after the onset of infection for an individual with the symptom compared to an individual without the symptom i.e. prolonged RTT

^Numbers were too few for further analyses

RTT, return to training

The following specific symptoms were associated with a more prolonged RTT (% lower chance) compared to athletes without the symptom: “chills” (50%; p=0.007), “abdominal pain” (50%; p=0.029), “loss of appetite” (40%; p=0.002), “difficulty in breathing” (40%; p=0.030), “hoarseness” (40%; p=0.043), “chest pain/pressure” (40%; p=0.044) and “excessive fatigue” (30%; p=0.026).

The association between the presence and number of symptoms by anatomical region and prolonged return to training (univariate models)

Associations between the presence and number of symptoms by anatomical region and prolonged RTT were explored in two univariate models. The Hazard Ratio (HR and 95%CI) for the presence and number of symptoms by anatomical region and prolonged return to training (RTT) is shown in Table 4.

Table 4: The Hazard Ratio (95%CI) for symptoms (presence and number) by anatomical region and prolonged return to training (RTT) (n=207) (Univariate models)

Symptoms by anatomical region	n (%) or Q1;median;Q3	Hazard Ratio (95%CI) *	Chi-Square	p-value
Presence of symptoms [β] (univariate model 1)				
Nose and Throat	190 (91.8)	0.9 (0.5-1.6)	0.07	0.791
Chest and Neck	169 (79.7)	0.6 (0.4-0.8)	8.34	**0.004**
Whole Body [^]	165 (79.7)	0.6 (0.4-0.9)	5.03	**0.025**
Number of symptoms [φ] (univariate model 2)				
Nose and Throat	2;3;4	0.89 (0.81-0.98)	6.2	**0.013**
Chest and Neck	1;2;3	0.88 (0.80-0.97)	6.45	**0.011**
Whole Body [^]	1;2;4	0.86 (0.79-0.94)	10.26	**0.001**
All symptoms	4;6;10	0.94 (0.90-0.98)	10.8	**0.001**

* Hazard Ratio of the hazard of RTT for an individual with either the presence or an increased number of symptoms in each anatomical region. HR<1 indicates a lower chance of RTT after the onset of infection

[β] Hazard of RTT for the presence of any symptoms compared to the hazard of RTT without the presence of any symptoms in each anatomical region

[φ] For number of symptoms the hazard ratio indicates the change in the risk for 1 more symptom

^ Includes 160 participants with "whole body" symptoms plus 5 with "other whole body" symptoms

RTT, return to training

The presence of any "nose and throat" symptoms (HR=0.9; 95%CI 0.5-1.6: p=0.791) was not associated with more prolonged RTT. The presence of any "chest and neck" (HR=0.6; 95%CI 0.4-0.8: p=0.004) and "whole body" symptoms (HR=0.6; 95%CI 0.4-0.9: p=0.025) were associated with more prolonged RTT.

In athletes with recent SARS-CoV-2 infection, the number of symptoms in each anatomical region was significantly associated with more prolonged RTT as follows: "nose and throat" symptoms (HR=0.89; 95%CI 0.81-0.98: p=0.013), "chest and neck" symptoms (HR=0.88; 95%CI 0.80-0.97: p=0.011), "whole body" symptoms (HR=0.86; 95%CI 0.79-0.94: p=0.001) and "all symptoms" (HR=0.94; 95%CI 0.90-0.98: p=0.001).

Factors associated with prolonged RTT following SARS-CoV-2 infection (multiple models)

In a multiple model including the significant demographic factors, only hours of training in the 7 days prior to infection was significant (p=0.017). Thus, associations between 1) the presence and 2) the number of symptoms by anatomical region, and prolonged return to training were explored in two multiple models adjusting for training hours in the 7 days before the onset of the infection. The adjusted Hazard Ratios (HR and 95%CI) for presence (model 1) and number of symptoms (model 2) by anatomical region in athletes, is shown in Table 5.

Table 5: The Hazard Ratio (95%CI) for symptoms (presence and number) by anatomical region and prolonged return to training (RTT) adjusted for training hours in the 7 days before the onset of infection (n=207) (Multiple models)

Symptoms by anatomical region	n (%) or Q1;median;Q3	Hazard Ratio (95%CI) *	Chi-Square	p-value
Presence of symptoms [β] (multiple model 1)				
Nose and Throat	190 (91.8)	0.87 (0.52-1.48)	0.28	0.597
Chest and Neck	169 (79.7)	0.60 (0.40-0.90)	6.08	**0.014**
Whole Body [^]	165 (79.7)	0.71 (0.47-1.08)	2.55	0.11
Number of symptoms [φ] (multiple model 2)				
Nose and Throat	2;3;4	0.89 (0.81-0.98)	5.59	**0.018**
Chest and Neck	1;2;3	0.89 (0.81-0.99)	5.04	**0.025**
Whole Body [^]	1;2;4	0.88 (0.80-0.96)	7.84	**0.005**
All symptoms	4;6;10	0.94 (0.91-0.98)	8.73	**0.003**

* Hazard Ratio of the hazard of RTT for an individual with either the presence or an increased number of symptoms in each anatomical region. HR<1 indicates a lower chance of RTT after the onset of infection

[β] Hazard of RTT for the presence of any symptoms compared to the hazard of RTT without the presence of any symptoms in each anatomical region

[φ] For number of symptoms the hazard ratio indicates the change in the risk for 1 more symptom

^ Includes 160 participants with "whole body" symptoms plus 5 with "other whole body" symptoms

RTT, return to training

In the first multiple model the presence of symptoms in the "nose and throat" as well as "whole body" symptoms were not predictive of prolonged RTT, but the presence of "chest and neck" symptoms was indicative of prolonged RTT (p=0.014). In the second multiple model, increasing number of symptoms in each anatomical region, remained predictors of prolonged RTT ("nose and throat"; HR=0.89; 0.81-0.98; p=0.018: "chest and neck"; HR=0.89; 0.81-0.99; p=0.025: "whole body"; HR=0.88; 0.80-0.96; p=0.005). Increasing number of "all symptoms" was also a predictor of prolonged RTT (HR=0.94; 0.91-0.98; p=0.003).

Finally, we explored the interaction of the total number of symptoms and number of symptoms in the 3 anatomical regions with the covariate "*training hours in the 7 days before the onset of symptoms*". None of the interactions were significant ($p>0.1$).

5.5 DISCUSSION

The aim of this study was to identify factors predictive of prolonged RTT following SARS-CoV-2 infection in athletes. Overall, in athletes that did start training, the median RTT was 14 days (interquartile range of 10-21 days). In our univariate models, we firstly show that females, symptoms by anatomical region ("chest and neck" or "whole body") and specific symptoms of SARS-CoV-2 were associated with prolonged RTT. Specific symptoms associated with more prolonged RTT were: "chills", "abdominal pain", "loss of appetite", "difficulty in breathing", "hoarseness", "chest pain/pressure" and "excessive fatigue". Secondly our univariate analysis showed that the number of symptoms in each anatomical region and reduced training in the 7 days prior to infection were predictive of prolonged RTT. In multiple models, including reduced training in the 7 days prior to infection, an increase in the number of symptoms in each anatomical region remained predictive of prolonged RTT. Factors not associated with prolonged RTT were age, level of sport participation, type of sport and a history of co-morbidities.

In our study, we clustered symptoms by anatomical region and added both the presence of any symptoms, and the number of symptoms in each anatomical region, into the multiple models. This analysis showed that not the presence of symptoms in anatomical regions, but rather that a greater number of symptoms in each region remained a significant predictor of prolonged RTT when adjusted for pre-infection training (hours in the 7 days before onset of infection). In the general population, a greater number of symptoms during acute phase is associated with increased risk of prolonged symptoms ("Long-Covid").[14 15] Our finding that greater number of symptoms is a predictor of prolonged RTT, may have potential clinical application in determining the severity of acute respiratory infections in athletes. Our study population was unvaccinated against SARS-CoV-2 and the predominant variants of SARS-CoV-2 during our study period were the ancestral virus (first wave) and the beta-variant (second wave). We acknowledge that previous SARS-CoV-2 infection, vaccination status and the variant could influence predictors of RTT following SARS-CoV-2 infection in athletes. Our results are thus strictly applicable only to 1) an unvaccinated SARS-CoV-2 naïve athletic

population, and 2) to infection with the SARS-CoV-2 variants that were predominant during our study period. There are data indicating that both the variant and the vaccination status may have an influence on the symptoms experienced and disease severity.[16 17] Despite this limitation of generalizability, we believe the findings of predictors of RTT in athletes are of value because they are novel and are valid for an investigation of this nature. We strongly encourage future studies to determine if these predictors are applicable to other athlete populations (vaccinated and unvaccinated) that are infected with other SARS-CoV-2 variants or with other pathogens causing acute respiratory infections.

Reduced training hours in the 7 days before symptom onset was associated with prolonged RTT in our univariate analysis. In our multiple models, reduced hours of training in the 7 days before the onset of SARS-CoV-2 infection, remained an independent predictor of prolonged RTT. This finding is of particular interest and is in keeping with several recently published findings that higher levels of physical activity per week are associated with reduced severity of SARS-CoV-2 infections.[18 19 20] The potential mechanism/s for this is not well-established but may be related to the immunoprotective effect of regular exercise.[21 22] However, we acknowledge that in this cross-sectional study, we cannot infer causality and athletes with higher pre-infection hours of training might, for example, be more determined to continue with sporting activity after acute infection, and therefore resume training sooner. In our univariate analysis of symptoms, we found that regional symptoms (any "chest and neck" symptoms and "whole body" symptoms) as well as selected specific symptoms, were predictive of delayed RTT. These findings correlate with data from our previous AWARE study.[6] In support of this finding, other published data also show that "chest pain" is associated with a higher likelihood of time loss (days from symptom onset to full training and competition) for more than 28 days, and athletes presenting with the presence of chest-related symptoms ("chest pain", "dyspnoea" and "cough") and "fever", were 2.1 (95%CI; 1.2-3.5) times more likely to have a prolonged time loss from training (more than 28 days). The same study showed an association between symptom duration lasting more than 28 days, with time loss for longer than 28 days.[23] The presence of symptoms indicative of regional or systemic illness, and their duration, may thus have an impact on time to RTT.

Finally, from our univariate analysis, we show that females have a higher chance of prolonged RTT after SARS-CoV-2 infection, but this was not significant in the multiple model analysis. To our knowledge, female sex has not been associated with delayed RTT in

the current literature. However, previous studies have found female athletes have a longer duration of symptoms during acute infection.[24] More specifically, the duration of SARS-CoV-2 symptoms lasted longer in females international-level athletes, compared to their male counterparts.[23] A study in the general population, also found females to be more prone to 'Long-COVID' (symptoms lasting for more than 28 days).[14] Furthermore, in an epidemiological study on the incidence of illness in athletes, females have been found to be more prone to infection.[1 25] Although these studies may indicate increased likelihood for females to have symptoms for longer and thus possibly delayed resumption of sport, we could not confirm this finding and it requires further investigation.

A strength of our study is that we included data from a sample of athletes with SARS-CoV-2 infection that was large enough to determine independent factors predictive of more prolonged RTT using multiple models. We acknowledge that our study has several limitations. Firstly, our sample was a convenience sample with potential selection bias. Secondly, participants were reliant on recall to document self-reported symptoms on an electronic questionnaire. However, this survey was conducted at a time of global heightened awareness of COVID-19, including COVID-19 related symptoms. Athletes, specifically professional and high level athletes, are particularly aware of their training schedules and any symptoms they experience (presence, duration and severity) and we are reasonably confident that recall of training data and symptoms is accurate. We also note that most published manuscripts reporting COVID-19 symptoms, in the general population and in athletes, relied on self-reporting of symptoms. Thirdly, we acknowledge that during data collection, 23 participants (11%) did not disclose their sex and this could have influenced our finding on female sex as a possible predictor of prolonged RTT in our univariate analysis. Although we do note that the median RTT was not significantly different between the groups that reported sex, and those who did not ($p=0.160$), we still suggest that the finding of sex as a possible predictor of RTT should be interpreted with caution. Our study design was cross-sectional, and although we show significant associations with prolonged RTT, these do not infer a cause-and-effect relationship.

These data are of clinical value to physicians responsible for athlete medical care and may develop into a predictive tool for RTT that can be used at the time of the initial consultation with the athlete.

5.6 CONCLUSION

In summary, our study shows that decreased hours of training in the 7 day-period before the onset of infection, as well as total number of symptoms and number of symptoms by anatomical region at the time of the acute infection, can predict prolonged RTT in an unvaccinated athlete with recent SARS-CoV-2 infection (ancestral virus and beta-variant). Age, level of sport participation, type of sport and history of co-morbidities were not predictive of RTT. These data can assist physicians responsible for athlete medical care as well as athletes or coaches, in planning and guiding RTT in athletes after SARS-CoV-2 infection. Future studies are needed to determine if these predictors are applicable to other athlete populations e.g. 1) vaccinated / unvaccinated, 2) athletes infected with other SARS-CoV-2 variants, and 3) athletes infected with other pathogens causing acute respiratory infections.

What are the new findings?

In unvaccinated athletes with recent SARS-CoV-2 infection (ancestral virus and beta-variant):

- Age, level of sport participation, type of sport and history of co-morbidities are not predictive of prolonged return to training (RTT)
- Reduced hours of training in the 7-day period before the onset of infection can predict prolonged RTT
- An increase in the total number of symptoms and the number of symptoms by anatomical region at the time of the acute infection, can predict prolonged RTT

Practical Implications

In the initial assessment of the athlete with a recent SARS-CoV-2 infection, the history of the total number of symptoms and number of symptoms per anatomical region during the acute phase, as well as training history in the period before the acute infection, may identify athletes with prolonged time course to RTT.

Data sharing statement

No additional data are available

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Competing Interests

None declared. The results of the present study do not constitute endorsement by ACSM and are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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List of Supplementary Digital Content

- Supplementary Digital Content 1.docx

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In Chapter 5, factors associated with time to return to training (RTT) in athletes with recent SARS-CoV-2 infection were determined. However, before an athlete can resume training, the sport and exercise medicine physician should medically clear the athlete, if indicated, to reduce the risk of potential medical complications during exercise. Multiple organ systems are under increased physiological stress during exercise.

In order to provide medical guidance on RTT, the severity of the recent SARS-CoV-2 infection should first be determined. More importantly, evidence of multi-organ involvement in the post-infection period should be investigated.

Current literature on the medical evaluation of athletes with a recent SARS-CoV-2 infection, mainly focused on the cardiovascular system, with limited data on assessment of other organ system involvement.

In Chapter 6, evidence of multi-organ involvement (residual symptoms, abnormal clinical signs and abnormal laboratory investigations) in athletes with recent SARS-CoV-2 infection are investigated and reported.

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CHAPTER 6: Manuscript information

Title of manuscript

Number of acute symptoms is associated with multi-organ involvement in athletes with recent SARS-CoV-2 infection: AWARE VII

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CHAPTER 6: CONFERENCE PRESENTATION

Title

Frequency of multi-organ involvement in athletes assessed 10-28 days after onset of SARS-CoV-2 infection

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CHAPTER 6

Number of acute symptoms is associated with multi-organ involvement in athletes with recent SARS-CoV-2 infection: AWARE VII

6.1 ABSTRACT

Purpose

Evidence of multi-organ involvement in athletes with recent SARS-CoV-2 infection is limited. This study determined the frequency (%) of multi-organ involvement and explored if greater number of symptoms during acute SARS-CoV-2 infection was associated with demographics, sport type, history of co-morbidities and multi-organ involvement.

Methods

95 athletes (18-60 years) underwent medical assessment 10-28 days after SARS-CoV-2 infection. Frequency (% athlete assessments) of organ system involvement (defined as residual symptoms, or abnormal clinical signs on physical examination or selected laboratory investigations) is reported. Participants were divided into three subgroups by number of symptoms during the acute infection (1=≤5, 2=6-9, or 3=≥10). Group differences were explored for: demographics, sport participation, history of co-morbidities and multi-organ involvement [frequency (%), number of organs].

Results

There was evidence of multi-organ involvement in 93-100% of athlete assessments, mostly residual symptoms (87%). Greater number of symptoms during the acute infection (subgroup 3 vs. 1) was associated with: females ($p=0.007$), endurance athletes ($p=0.022$), and increased % organ involvement ($p<0.001$) per athlete assessment. After adjusting for sex, type of sport, and co-morbidities, number of organ systems involved was greater in subgroup 2 vs. 1 ($p=0.002$) and 3 vs. 1 ($p<0.001$)

Conclusion

More acute SARS-CoV-2 symptoms in athletes (>5) was associated with higher frequency and number of multi-organ involvement, independent of other variables (sex, type of sport,

history of co-morbidities). Number of acute symptoms is a valuable measure of disease severity, which is the first step in clinical return to sport (RTS) decision making after recent SARS-CoV-2 infection.

6.2 INTRODUCTION

Acute respiratory infections (ARinf) are a common cause of illness in athletes[1-4] with approximately 20% of ARinf resulting in time loss in training/competition.[5] Time loss (number of days lost to training/competition), is a recognised parameter to estimate severity of illness in athletes.[6] The sport and exercise medicine (SEM) physician regularly makes important decisions when athletes can safely return to sport (RTS) after ARinf. Return to sport (RTS) after ARinf is a continuum[7] starting with return to training (RTT), then progresses to full performance (RTFP), thus full RTS. An International Olympic Committee (IOC) consensus group recently proposed an algorithm for RTS decisions after ARinf in athletes[8]. The first step is to determine the severity of the infection based on two important parameters: 1) symptom characteristics during the acute phase of the infection, and 2) evidence of multi-organ involvement.[8]

Early data on symptom characteristics of SARS-CoV-2 infection showed acute symptom clusters/types can influence RTT.[9 10] There is some evidence that, in the general population, total number of acute symptoms of SARS-CoV-2 infection ≥5 is associated with residual "long-COVID"[11 12] There is recent evidence that total number of acute symptoms of SARS-CoV-2 infection in athletes is an indicator of prolonged RTT[13]. Therefore, the total number of acute symptoms of SARS-CoV-2 infection in athletes may be an important predictor of more severe illness.

SARS-CoV-2 infection was initially regarded primarily as a respiratory disease, but emerging evidence in the general population indicates that multiple organ systems can be affected.[14 15] In the general population, older age, male sex, high body mass index (BMI) and history of co-morbidities are factors associated with greater risk of multi-organ involvement.[16 17] To date, studies in athletes mostly focused on cardiovascular system involvement.[18-20] Data on the frequency of multi-organ involvement and factors associated with multi-organ involvement of SARS-CoV-2 infection in athletes are limited. For example, the relationship

between total number of acute symptoms of SARS-CoV-2 infection in athletes and multi-organ involvement has not been studied.

The aims of the study were to determine the frequency (%) of multi-organ involvement (residual symptoms, abnormal clinical signs on physical examination, or abnormal laboratory investigations) among athletes assessed 10-28 days after acute SARS-CoV-2 infection, and explore if a greater total number of symptoms during the acute SARS-CoV-2 infection phase was associated with demographics, sport participation, history of co-morbidities and multi-organ involvement (frequency and number of organs involved).

6.3 METHODS

Study design and setting

This is a prospective cohort study that is part of the **A**thletes **W**ith **A**cute **R**espiratory Inf**E**ctions (AWARE) studies. The Sport, Exercise Medicine and Lifestyle Institute (SEMLI), at the University of Pretoria, South Africa, established a COVID-19 Recovery Clinic to medically assess athletes with recent SARS-CoV-2 infections. The study was conducted from July 2020 to October 2021. During this period, a 10-day period of self-isolation was advised and the most prevalent SARS-CoV-2 variants were the Ancestral virus, Beta and Delta variants. Ethical clearance was obtained from the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria (REC 409/2020 and REC 751/2019).

Study participants

A total of 95 athletes were deemed eligible to participate, fulfilling the inclusion criteria: 1) aged 18-60 years, 2) confirmed SARS-CoV-2 infection (10-28 days since onset of symptoms), 3) competitive athletes (varying participation levels/sport types), and 4) gave written informed consent. Most athletes (94%) were unvaccinated against SARS-CoV-2 as vaccination was rolled out in phases (early 2021) and not accessible to all age groups during the study period.

Data collection

Data collection took place during a medical assessment 10-28 days after onset of symptoms, using a standardised format to collect medical history, residual symptoms, clinical signs, and

selected laboratory investigations to determine evidence of multi-organ involvement (frequency and number of organ systems).

Medical history

Athletes completed a standardised online questionnaire,[9] captured on Research Electronic Data Capture (REDCap),[21 22] with the following sections:

Demographics: Age, sex, weight, and height (for BMI calculation)

Sports participation: Level of sport participation and type of sport[23]

History of co-morbidities: History of co-morbidities by organ systems (cardiovascular disease/risk, respiratory, nervous, psychological, gastrointestinal, metabolic, renal, immune/blood system, and cancer).

Self-reported symptoms during the acute phase of infection: Symptom characteristics (type, duration and severity) of 26 potential symptoms during the acute phase of infection, which were grouped by organ system/anatomical region.[9]

Residual symptoms determined at the time of the medical assessment: Residual symptoms were defined as those symptoms still present at the time of the medical assessment and were categorised by organ system.

Clinical signs on physical examination

Abnormal clinical signs were recorded, by organ system (cardiovascular, respiratory, neurological, gastrointestinal, musculoskeletal, immunological/haematological, ocular, skin, systemic), during a standardised physical examination (Supplementary File A).

Laboratory investigations

Laboratory investigations were performed in all athletes and grouped, by organ system, as follows:

<u>Cardiovascular</u>

Resting electrocardiogram (ECG): A 12-lead resting ECG was performed and exercise-related adaptive changes ('athlete's heart') were considered normal.

Sub maximal exercise ECG: A sub-maximal exercise test (modified Bruce protocol up to stage 5) were done on all participants after contra-indications for exercise were excluded.[24] Interpretation of all ECG findings followed published guidelines[25 26] and abnormalities were confirmed by a cardiologist (MM).

Resting echocardiogram (ECHO): Transthoracic ECHO evaluation included left ventricular ejection fraction (LVEF),[27] ventricular wall motion abnormalities and pericardial effusions.
High sensitivity cardiac troponin T (hs-cTnT): hs-cTNT was analysed on venous blood samples.
Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE): CMR with LGE, was performed on a subset of 65 athletes, regardless of clinical presentation or other cardiac investigations. The main reasons for not conducting CMR on all athletes were: 1) that CMR was not available for research purposes in the early stage of the COVID-19 pandemic, and 2) although CMR was offered to all athletes once it became available, some athletes did not consent to having a CMR performed. CMR findings were reported by two radiologists experienced in CMR (LS, ADP). Myocardial/pericardial LGE, pericardial effusions, decreased LVEF[28] and wall motion abnormalities were individually recorded. LGE enhancement of hinge/insertion points were excluded.[29-31] References for T1 and T2 mapping were >1050ms and 55ms respectively.[32] Myocarditis was diagnosed by CMR, based on the modified Lake Louise criteria.[33] Individual abnormal CMR findings were grouped using the following reported definitions:[20 34] 1) definite cardiac involvement (T1 abnormality or LGE+T2 abnormality) OR 2) T2 abnormality plus ≥1 supportive findings (LVEF<45%, small/greater pericardial effusion, pericardial LGE or troponin >99% upper limit of normal), 2) probable cardiac involvement [(T1 abnormality OR presence of LGE plus ≥1 supportive findings (similar as definite)], 3) possible cardiac involvement (isolated T1 abnormality or presence of LGE), and 4) pericardial involvement (small/greater pericardial effusion OR pericardial LGE).

Respiratory

Pulmonary function tests (PFT): Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded at rest. Results below the lower limit of normal (LLN)[35] of calculated values were regarded as abnormal.

Other organ systems

Evidence of other organ system involvement was determined by abnormalities in the following blood tests:
Gastrointestinal: Aspartate transaminases (AST), alanine transaminases (ALT)
Musculoskeletal: Creatine kinase (CK)

Immunological/haematological: Total white cell count (WCC), neutrophil/lymphocyte counts and C-Reactive Protein (CRP)

Definition of multi-organ involvement and calculation of number of organs involved

We defined involvement in any one of nine organ systems as the presence of any of the following abnormalities in an organ system, at the time of the medical assessment: 1) residual symptoms, or 2) abnormal clinical signs on physical examination, or 3) abnormal laboratory investigations. The number of organ systems involved per assessment was calculated as the total number of organ system abnormalities, e.g. if an athlete assessment revealed a residual respiratory symptom, and two abnormalities in the cardiovascular system e.g. chest pain (symptom) and an abnormal resting ECG (abnormal laboratory investigation), the number of organs involved was calculated as 2 (organ system counted once, despite number of abnormalities). The number of organs involved were also explored in three ways, based on involvement of the respiratory system (upper and lower) as follows: 1) any organ system involvement (including the respiratory system), 2) organ system involvement (excluding the upper respiratory system), and 3) organ system involvement (excluding the respiratory organ system).

Classification of athletes in three subgroups based on total number of symptoms during the acute phase of the infection

We categorized the athletes into three subgroups based on total number of symptoms during the acute phase of the infection:

Based on emerging data linking the total number of acute symptoms of SARS-CoV-2 infection to "Long COVID-19" in the general population,[11 12] and to prolonged RTT[13] (a proxy for infection severity) in athletes we categorized the participants into three subgroups:

Subgroup 1: Total number of symptoms during the acute phase of the infection ≤ 5

Subgroup 2: Total number of symptoms during the acute phase of the infection 6 - 9

Subgroup 3: Total number of symptoms during the acute phase of the infection ≥ 10

Patient and public involvement (PPI)

Athletes, as well as medical practitioners treating ARinf, were requested to give feedback on the questionnaire in the developing stages.

Measures of outcome

The main measures of outcome were to determine: 1) the frequency (% of athletes) with evidence of multi-organ involvement, based on residual symptoms or abnormal clinical signs/laboratory investigations 10-28 days after SARS-CoV-2 infection, and 2) differences between three subgroups (based on total number of symptoms during the acute phase of the infection) for the following variables: demographics, sport participation, history of co-morbidities and multi-organ involvement (frequency and number of organ systems involved).

Statistical analysis of data

Data were analysed using SAS (v 9.4). Demographics, sport participation and history of co-morbidities were described for the 95 athletes using n (%) or mean (SD). Two participants had re-infections. Models were adjusted for duplicate assessments. Variables were reported for 96 athlete assessments with the exception of CMR (n=65). Missing data were reported on in each variable. Data on missing CMR data (n=31), are reported for both lower (all missing CMR counted as "normal") and upper bound (all missing CMR counted as "missing'). Acute symptom number subgroups (1=≤5, 2=6-9, 3=≥10 symptoms) were compared for demographics, sport participation, co-morbidities and multi-organ involvement (number of organ systems involved). The following methods were used for: categorical variables (exact logistic regression), continuous variables (linear regression), number of co-morbidities (negative binomial distribution) and number of organ systems involved (Poisson distribution). In the linear regression model, global p-values for the F-statistic and pair-wise differences for the difference between the subgroups were reported. In the exact logistic regression model, global exact p-values for the subgroup differences and exact odds ratios were reported. The negative binomial distribution was used for analysis of number of co-morbidities involved. Chi-Square p-value for Type 3-analysis were reported for global test. For the pair-wise differences, the p-values for the z-statistic were reported. The Poisson distribution with error estimator (log link function) was used for analysis of any organ system involvement. The reference category for pair-wise comparisons between subgroups is subgroup 1 (≤5 symptoms). The data were adjusted for possible covariates in separate models for each co-variate, because data were too sparse to adjust for co-variates in one model. Statistical significance was accepted at $p<0.05$.

6.4 RESULTS

Ninety-five athletes were included in the study. One athlete had a recurrent SARS-CoV-2 re-infection (8 weeks apart) and both assessments were included; thus 96 athlete assessments were recorded. No athletes were hospitalised and 4 (4.2%) were asymptomatic. The median (interquartile range-IQR) days from onset of symptoms (positive test if asymptomatic) to the medical assessment was 17 (14.5;21) days.

Demographics, sport participation and history of co-morbidities for the study participants

The demographics, sport participation and co-morbidities for the study participants (n=95) are depicted in the Supplementary Table A.

The mean age of the athletes was 25 years, 63% were male, 46% were professional athletes and 55% competed in mixed sports. A history of co-morbidities was reported by 52%, mostly related to the respiratory tract (26%), specifically asthma (15%) and hay fever (16%). Other allergies (plant/animal material or medication) were reported by 23% of participants.

Frequency of multi-organ involvement among athletes presenting 10-28 days after acute SARS-CoV-2 infection

The frequency (% athlete assessments) of multi-organ involvement (residual symptoms or abnormal clinical signs or abnormal laboratory investigations) among athletes presenting 10-28 days after acute SARS-CoV-2 infection is summarised in Table 1. Variables are reported for all athlete assessments (n=96) except for CMR where only a subset (n=65) was available. Missing CMR (n=31) data were reported in two ways: 1) “normal CMR” (lower bound) or 2) “missing CMR” (upper bound).

Table 1: The frequency (% athlete assessments) of multi-organ involvement (residual symptoms or abnormal clinical signs/laboratory investigations) among athletes assessed 10-28 days after acute SARS-CoV-2 infection (by organ system)

Evidence of multi-organ involvement	**n (%)**
Any organ involvement *	**89/96 (92.7) ***
Any organ involvement **	**89/89 (100) ****
Residual symptoms [a] (any) **(n=96)**	**82 (87.2)**
Cardiovascular [b]	25 (26.3)
Respiratory (any) [b]	70 (73.7)
Upper respiratory	46 (47.9)
Lower respiratory [c]	55 (59.1)
Neurological	52 (54.2)
Gastrointestinal [b]	16 (16.8)
Musculoskeletal	10 (10.4)
Ocular [a]	5 (5.3)
Skin	0
Systemic [b]	0
Abnormal clinical signs (any) [d] **(n=96)**	**37 (45.7)**
Cardiovascular [e]	0
Respiratory (any) [f]	31 (35.6)
Upper respiratory [f]	31 (35.6)
Lower respiratory	0
Neurological	0
Gastrointestinal [g]	9 (9.9)
Musculoskeletal	0
Ocular [a]	3 (3.2)
Skin	2 (2.1)
Systemic	0
Abnormal laboratory investigations (any) [b] ****	**57/95 (60) ***
Abnormal laboratory investigations (any) [h] ****	**57/76 (75)** **
Cardiovascular (any) [b] *	29/95 (30.5)
Cardiovascular (any) [j] **	29/66 (43.9)
Electrocardiogram (resting/exercise) [b]	9 (9.4)
Echocardiogram [b]	3 (3.2)
High-sensitivity Troponin T [a]	0
CMR abnormalities (in subgroup of 65 participants)	20/65 (30.8)
Respiratory (any) [j]	6 (6.4))
Resting pulmonary function test (PFT)[a]	6 (6.4)
Gastrointestinal (any)	22 (22.9)
Aspartate transaminase (AST)	16 (16.7)
Alanine transaminase (ALT)	14 (14.6)
Musculoskeletal	10 (10.8)
Creatine kinase (CK)	10 (10.8)
Immunological/haematological	10 (10.4)

White cell count (WCC)	6 (6.3)
Neutrophil count	7 (7.3)
Lymphocyte count	0
C-Reactive Protein (CRP) [b]	1 (1.1)

*Values (n and %) reported when all missing CMR (n=31) were treated as a "normal" CMR (lower bound)
** Values (n and %) reported when all missing CMR (n=31) were treated as a "missing" CMR (upper bound)
CMR, cardiac magnetic resonance
Missing data on participants: a=2; b=1, c=3, d=15, e=6, f=9, g=5, h=20, i=4, j=30

If all missing CMR data were treated as "normal" (lower bound), there was evidence of multi-organ involvement in 93% of assessments, with residual symptoms in 87%, abnormal clinical findings in 46%, any abnormal laboratory investigations in 60%. If all missing CMR values were treated as "missing" (upper bound) there was evidence of multi-organ involvement in 100% of assessments, any abnormal laboratory investigations in 75%, and abnormal cardiovascular system laboratory investigation 44%.

Residual symptoms

The most frequent residual symptoms were in the respiratory system (74%). Higher frequencies of residual symptoms (>15% of assessments) were shortness of breath (33%), dry cough (23%), chest tightness (16%) and dyspnoea (16%) for the lower respiratory and blocked nose (20%) and sinus pressure (20%) confined to the upper respiratory. The most common neurological symptoms were loss/altered smell (27%) or taste (24%), excessive fatigue (23%) and headache (19%). More frequent cardiovascular related symptoms were racing heart (23%) and chest pain (13%). Detailed individual residual symptoms are presented in the Supplementary Table B Section 1.

Abnormal physical examination

The physical examination was abnormal in 46% athletes, mostly in the upper respiratory tract (36%), followed by abdominal tenderness (10%). Detailed findings are in the Supplementary Table B Section 2.

Abnormal laboratory *investigations*

CMR with LGE was performed a median (IQR) of 29 (23; 33.5) days after the onset of symptoms in a subset of 65 (68%) participants. 17 Athletes had CMR-defined criteria for cardiac involvement[20 34] (1 definite, 5 probable, 6 possible and 5 pericardial). 3 Participants had isolated decreased LVEF.[28] Cardiomyopathy (hypertrophic and non-compaction) was identified in 2 athletes. Neither had any cardiopulmonary symptoms and as these conditions

were likely hereditary in origin, their CMR, ECHO, and ECG findings were not reported as abnormalities in the cardiovascular system related to SARS-CoV-2 infection. In summary, abnormal CMR findings were reported in 31% (20/65) of participants where CMR was performed. Individual abnormalities are reported in Supplementary Table B Section 4)

Other abnormalities in the cardiovascular system were resting ECG (2%), exercise ECG (8%) and ECHO (3%). All hs-cTnT results were within normal limits. If all missing CMR data were treated as "normal" (lower bound), abnormal findings on laboratory investigations were present in 60% of athletes and abnormal cardiovascular system laboratory investigation in 31% athletes. If all missing CMR data were treated as "missing" (upper bound), abnormal findings on laboratory investigations were present in 75% of athletes, with abnormal cardiovascular system laboratory investigations in 44% athletes. Detailed individual findings are summarised in Supplementary Table B Section 3 and 4.

Factors associated with total number of symptoms during the acute phase of the infection in three subgroups

Demographic, sport participation, and co-morbidities

Demographic, sport participation, and co-morbidities in the three subgroups, based on number of symptoms during the acute phase of the infection, are depicted in Table 2.

Table 2: Demographic, sport participation, and co-morbidities in three subgroups, based on total number of symptoms during the acute phase of the infection (n=95)

Variables	Subgroup 1 (≤5 acute symptoms) (n=29)	Subgroup 2 (6-9 acute symptoms) (n=34)	Subgroup 3 (≥10 acute symptoms) (n=32)	p-value (2 vs. 1)	p-value (3 vs. 1)	p-value (difference between subgroups)
Demographics						
Age (years) (mean) (SD)	23.4 (6.7)	25.1 (6.5)	26.3 (7.9)	0.751	0.251	0.283
Sex						
Male, n (%)	25 (86.2)	19 (55.9)	16 (50.0)	0.017 *	0.005 **	0.007
Female, n (%) (ref)	4 (13.8)	15 (44.1)	16 (50.0)			
BMI (mean) (SD)	25.1 (3.5)	24.1 (4.0)	23.9 (4.2)	0.969	0.453	0.447
Sport participation						
Level of sport participation						
Professional n (%)	19 (65.5)	13 (38.2)	12 (37.5)	0.056	0.053	0.048
Amateur n (%)	10 (34.5)	21 (61.8)	20 (62.5)			
Type of sport						
Endurance [#] n (%)	7 (24.1)	18 (52.9)	18 (56.3)	0.037 *	0.021 **	0.022
Mixed [α] (including skills [β] n=2 and power [¥] n=7) n (%)	22 (75.9)	16 (47.1)	14 (43.8)			
History of co-morbidities						
Number of co-morbidities per participant, mean (SD)	1.2 (1.4)	0.5 (0.8)	1.7 (2.0)	0.020 *	0.25	0.003
Individual co-morbidities by organ system						
Cardiovascular	3 (10.3)	3 (8.8)	2 (6.3)	-		-
Risk factors cardiovascular disease [a]	4 (14.3)	3 (8.8)	4 (12.5)			
Respiratory	8 (27.6)	5 (14.7)	12 (37.5)			
Nervous system	1 (3.5)	1 (2.9)	3 (9.4)	-	-	-
Psychological disorders	2 (6.9)	1 (2.9)	6 (18.8)	-	-	-
Gastrointestinal	5 (17.2)	1 (2.9)	5 (15.6)	-	-	-
Metabolic	0	1 (2.9)	2 (6.3)	-	-	-
Renal or bladder	0	0	1 (3.1)	-	-	-
Immune/blood system	1 (3.5)	1 (2.9)	3 (9.4)	-	-	-
History of growths/cancer	1 (3.5)	0	1 (3.1)	-	-	-
Allergies (yes) n (%)	4 (13.8)	6 (17.7)	12 (37.5)	-	-	-

* p<0.05 subgroup 2 vs. 1
** p<0.05 subgroup 3 vs. 1
- Numbers too small to test statistical significance
[#] Cycling, mid/long distance swimming/running, triathlon
[α] Rugby, field hockey, soccer, tennis
[β] Golf
[¥] Short distance running, shot put, javelin, discus, gymnastics, judo
Missing data on participants: a=1

Age and BMI were not different between subgroups. There was a significantly higher % of females (p=0.007) in subgroup 3 vs. 1 (p=0.005) or 2 (p=0.017). There was a significantly higher % of endurance athletes in subgroups 2 (p=0.037) and 3 (p=0.021) vs. 1. The mean number of co-morbidities (p=0.003) was significantly lower in subgroup 2 compared with subgroup 1 (p=0.02).

Frequency of multi-organ involvement in three subgroups

The frequency (% athletes) of multi-organ involvement (residual symptoms, abnormal clinical signs and laboratory investigations) in the three different subgroups based on total number of symptoms during the acute phase of the infection is shown in Table 3.

Table 3: The frequency (% athletes) of multi-organ involvement (residual symptoms, abnormal clinical signs/laboratory investigations) in three different subgroups based on total number of symptoms during the acute phase of the infection (n=96)

Evidence of multi-organ involvement per organ system	Subgroup 1 (≤5 acute symptoms) (n=30)	Subgroup 2 (6-9 acute symptoms) (n=34)	Subgroup 3 (≥10 acute symptoms) (n=32)	p-value (2 vs. 1)	p-value (3 vs. 1)	p-value (difference between subgroups)
Any organ involvement *	25 (26.0)	32 (33.3)	32 (33.3)	**0.223**	**0.068**	**0.179**
Any residual symptoms [a] (n=96)	21 (72.4) [b]	30 (90.9) [b]	31 (96.9) *	0.116	**0.017**	**0.011**
Cardiovascular (Any)	1 (3.3)	11 (33.3) [b]	13 (40.6)	-	-	-
Respiratory (Any) [b]	16 (55.2) [b]	25 (73.5)	29 (90.6)	0.208	**0.004 ****	**0.007**
Upper respiratory (Any)	12 (40.0)	10 (29.4)	24 (75.0)	0.531	**0.011 ****	**0.001**
Lower respiratory (Any) [c]	11 (39.3) [a]	22 (66.7) [b]	22 (68.8)	0.059	**0.042 ****	**0.040**
Neurological (Any)	12 (40.0)	17 (50.0)	23 (71.9)	0.583	**0.022 ****	**0.032**
Gastrointestinal (Any)	3 (10.0)	6 (18.2) [b]	7 (21.9)	-	-	-
Musculoskeletal (Any)	0	3 (8.8)	7 (21.9)	-	-	-
Ocular (Any)	0	3 (9.1) [b]	2 (6.5) [b]	-	-	-
Systemic (Any) [b]	0	0	0			
Any abnormal clinical signs [d] (n=96)	8 (34.8) [e]	11 (39.3) [f]	18 (60.0) [a]	-	-	-
Cardiovascular (Any) [f]	0	0	0			
Respiratory (Any) [g]	8 (29.6) [c]	8 (26.7) [h]	15 (50.0) [a]	-	-	-
Upper respiratory	8 (29.6) [c]	8 (26.7) [h]	15 (50.0) [a]	-	-	-
Lower respiratory	0	0	0			
Neurological (Any)	0	0	0			
Gastrointestinal (Any) [a]	0[c]	3 (9.1) [b]	6 (19.4) [b]	-	-	-
Skin (Any)	0	1 (2.9)	1 (3.1)	-	-	-
Ocular (Any) [c]	0	2 (6.1) [b]	1 (3.2) [a]	-	-	-
Any abnormal laboratory investigations [a] (n=96)*	15 (15.79)	23 (24.2)	19 (20)	0.1806	0.6273	0.2947
Cardiovascular (Any)[b] *	8 (8.42)	13 (13.68)	8 (8.42)	-	-	-
Respiratory (Any) [h]	0 [b]	4 (12.2) [b]	2 (6.7) [a]	-	-	-
Gastrointestinal (Any)	4 (13.3)	7 (20.6)	11 (34.4)	-	-	-
Musculoskeletal (Any) [c]	3 (10.0)	3 (9.4) [a]	4 (12.9) [b]	-	-	-
Immune/blood system (Any)	5 (16.7)	2 (5.9)	3 (9.4)	-	-	-

** p<0.05 subgroup 3 vs. 1
- Numbers too small to calculate p-value
* Values (n and %) reported when all missing CMR were treated as a "normal" CMR (lower bound)
CMR, cardiac magnetic resonance
Missing participants: a=2, b=1, c=3, d=15, e=7, f=6, g=9, h=4

The frequency of any residual symptoms (p=0.011), respiratory symptoms (p=0.007) and neurological symptoms (p=0.032) differed between subgroups. Specifically, in subgroup 3

vs. 1, there was a higher frequency of overall residual symptoms (p=0.017), residual respiratory (p=0.04) [upper (p=0.011) and lower (p=0.042)] and neurological symptoms (p=0.022). There were no significant differences between subgroups 1 and 2. Details of individual residual symptoms in subgroups are reported in Supplementary Table C Section 1. Although numbers were too few to determine statistical differences between all subgroups, we noted a general increase in frequency of residual symptoms from subgroup 1 to 3.

There was no statistically significant difference in the frequency of abnormal clinical signs by organ system between the subgroups. Again, the frequency of abnormal clinical signs generally increased from subgroup 1 to 3. Detailed frequency of abnormal clinical signs in subgroups are reported in Supplementary Table C Section 2.

The frequency of abnormal laboratory investigations, including CMR, did not differ between the subgroups and are reported in Supplementary Table C Section 3 and 4 respectively.

Number of organs per athlete assessment

The number [mean (SE)] of organs involved per athlete assessment is depicted in Table 4. This variable was determined for: 1) all organ system involvement (including the respiratory system), 2) organ system involvement (excluding the upper respiratory system), and 3) organ system involvement (excluding the respiratory organ system).

Table 4: Number (mean (SE)) of organ system involvement per athlete assessment in three different subgroups based on total number of symptoms during the acute phase of the infection (n=96)

Subgroups	n	Number of organs Mean estimate number (SE)	p-value (2 vs. 1)	p-value (3 vs. 1)	p-value (2 vs. 3)	p-value # (Differences between subgroups)
Organ system involvement (including the respiratory system)						
Subgroup 1 (≤5 symptoms)	30	1.3 (0.16)	-			**<0.0001**
Subgroup 2 (6-9 symptoms)	34	2.2 (0.19)	**0.0004**			
Subgroup 3 (≥10 symptoms)	32	2.6 (0.22)		**<0.0001**	0.154	
Organ system involvement (excluding upper respiratory tract)						
Subgroup 1 (≤5 symptoms)	30	1.0 (0.15)	-			**<0.0001**
Subgroup 2 (6-9 symptoms)	34	2.1 (0.20)	**<0.0001**			
Subgroup 3 (≥10 symptoms)	32	2.4 (0.23)		**<0.0001**	0.2986	
Organ system involvement (excluding the respiratory system: upper and lower)						
Subgroup 1 (≤5 symptoms	30	0.6 (0.13)	-			**<0.0001**
Subgroup 2 (6-9 symptoms)	34	1.4 (0.18)	**0.001**			
Subgroup 3 (≥10 symptoms)	32	1.7 (0.20)		**<0.0001**	0.302	

n= number of athlete assessments
# Global test

The number of organ systems involved were significantly and consistently higher in subgroup 3 vs. 1 in all three categories: 1) all organ system involvement (including the respiratory system) ($p<0.0001$), 2) organ system involvement (excluding the upper respiratory system) ($p=<0.0001$), and 3) organ system involvement (excluding the respiratory organ system) ($p<0.0001$). We performed a similar additional analysis using only the subgroup of 65 participants where we had complete CMR data, and this confirmed the results in Table 4 (data not shown).

The relationship between number of any organ system involved and the total number of symptoms during the acute phase of the infection is shown in Figure 1.

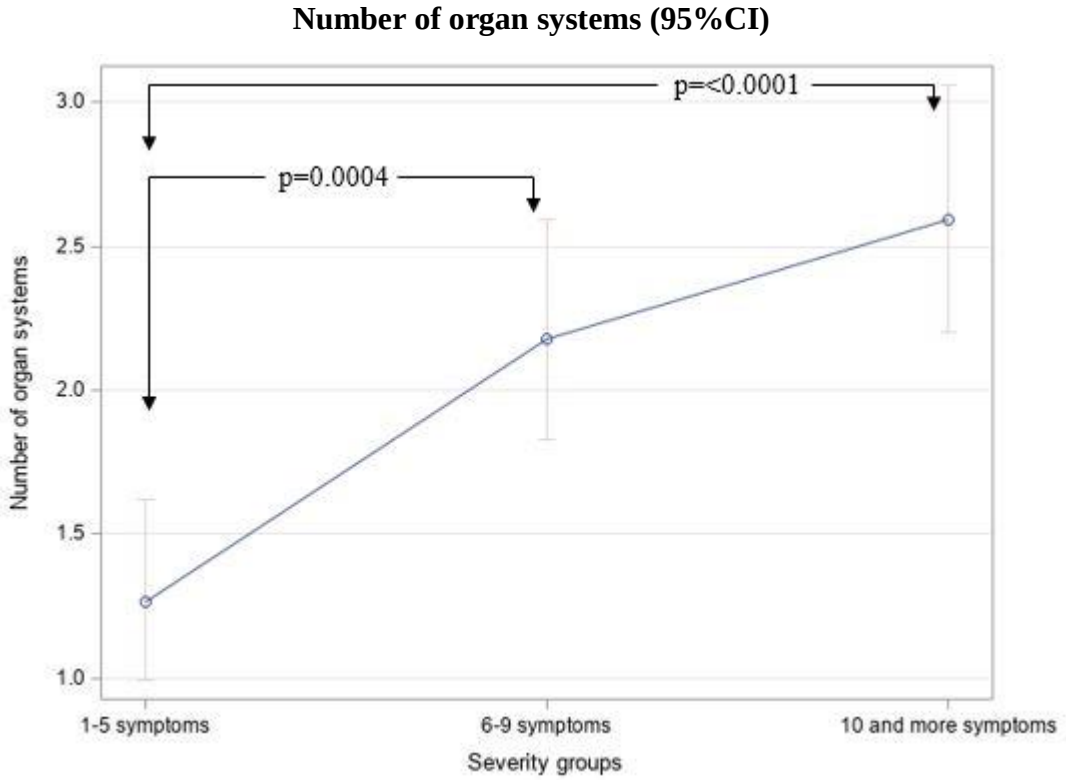

Figure 1: The relationship between the total number of symptoms during the acute phase of the infection and the number of organ systems involved (any residual symptom, clinical signs or laboratory investigations) assessed at 10-28 days after SARS-CoV-2 infection in athletes

The number of organ system systems involved was significantly higher in subgroup 2 ($p=0.0004$) and subgroup 3 ($p<0.0001$) compared to subgroup 1.

Additional data on the number (%) of individual organ systems involved in the different subgroups are reported in Table 5.

Table 5: Number (%) of individual organ systems involved in three different subgroups by total number of symptoms during the acute phase of the infection (n=96)

Organ system	Any organ involvement n (%)	Subgroup 1 (≤5 acute symptoms) (n=30) n (%)	Subgroup 2 (6-9 acute symptoms) (n=34) n (%)	Subgroup 3 (≥10 acute symptoms) (n=32) n (%)	p-value (2 vs. 1)	p-value (3 vs. 1)	p-value (All subgroups)
Cardiovascular (n=69) [#*]	45 (65.22)	8 (11.6)	21 (30.4)	16 (23.2)	-	-	-
Respiratory	76 (79.2)	19 (63.3)	27 (79.4)	30 (93.8)	0.251	**0.007**	**0.011**
Upper respiratory [a]	58 (65.9)	17 (63.0)	14 (45.2)	27 (90.0)	0.275	**0.033**	**0.0009**
Lower respiratory [b]	58 (62.4)	11 (39.3)	23 (69.7)	24 (75.0)	**0.033**	**0.011**	**0.010**
Neurological	52 (54.2)	12 (40.0)	17 (50.0)	23 (71.9)	**0.008**	**<0.0001**	**0.0002**
Gastrointestinal [c]	37 (41.1)	6 (22.2.)	14 (43.8)	17 (54.8)	-	--	-
Musculoskeletal	20 (20.8)	3 (10.0)	6 (17.7)	11 (34.4)	-	-	-
Ocular [d]	5 (5.4)	0	3 (9.4)	2 (6.7)	-	-	-
Skin	2 (2.1)	0	1 (2.9)	1 (3.1)	-	-	-
Immune	10 (10.4)	5 (16.7)	2 (5.9)	3 (9.4)	-	-	-
Systemic	0	0	0	0			

Cardiovascular findings included the CMR subset of 65 participants
* All missing CMR were treated as normal = lower bound
- Numbers too small to calculate p-value
CMR, cardiac magnetic resonance
Number of missing participants: a=8, b=3, c=6, d=4

In the upper respiratory (p=0.033), lower respiratory (p=0.011) and neurological systems (p<0.001), the number of organs involved in subgroup 3 was significantly greater than in subgroup 1. In the lower respiratory and neurological system, the number of organs involved in subgroup 2 was significantly greater than in subgroup 1.

6.5 DISCUSSION

The first main finding of this study is that evidence of multi-organ involvement, 10-28 days after onset of SARS-CoV-2 infections of Ancestral virus or Beta and Delta variants in predominately unvaccinated athletes, was very high (93-100%; dependant on the use of upper or lower bound values for missing CMR data). This was mostly due to residual symptoms (87%), abnormal laboratory investigations (60-75%; dependant on the use of upper or lower bound values for missing CMR data), and less frequently due to abnormal clinical signs (46%). We also found that female and endurance athletes have greater number of acute symptoms. The main novel finding was that in athletes with recent SARS-CoV-2 infection, greater total number of symptoms during the acute infection was associated with evidence of more multi-organ involvement (both increased frequency and greater number of organs

involved). This association remained significant when adjusted for individual co-variates (sex and number of co-morbidities) and when the analysis was performed in the subgroup of 65 participants with complete data (CMR subgroup).

Our first finding was that evidence of multi-organ involvement after recent SARS-CoV-2 infection in athletes was high, but we note that this was mainly due to residual symptoms (87%). Abnormal laboratory investigations were present in 60-75% of athletes, and approximately half of the athletes had abnormal clinical signs (46%). The evidence of multi-organ involvement is summarised in figure 2.

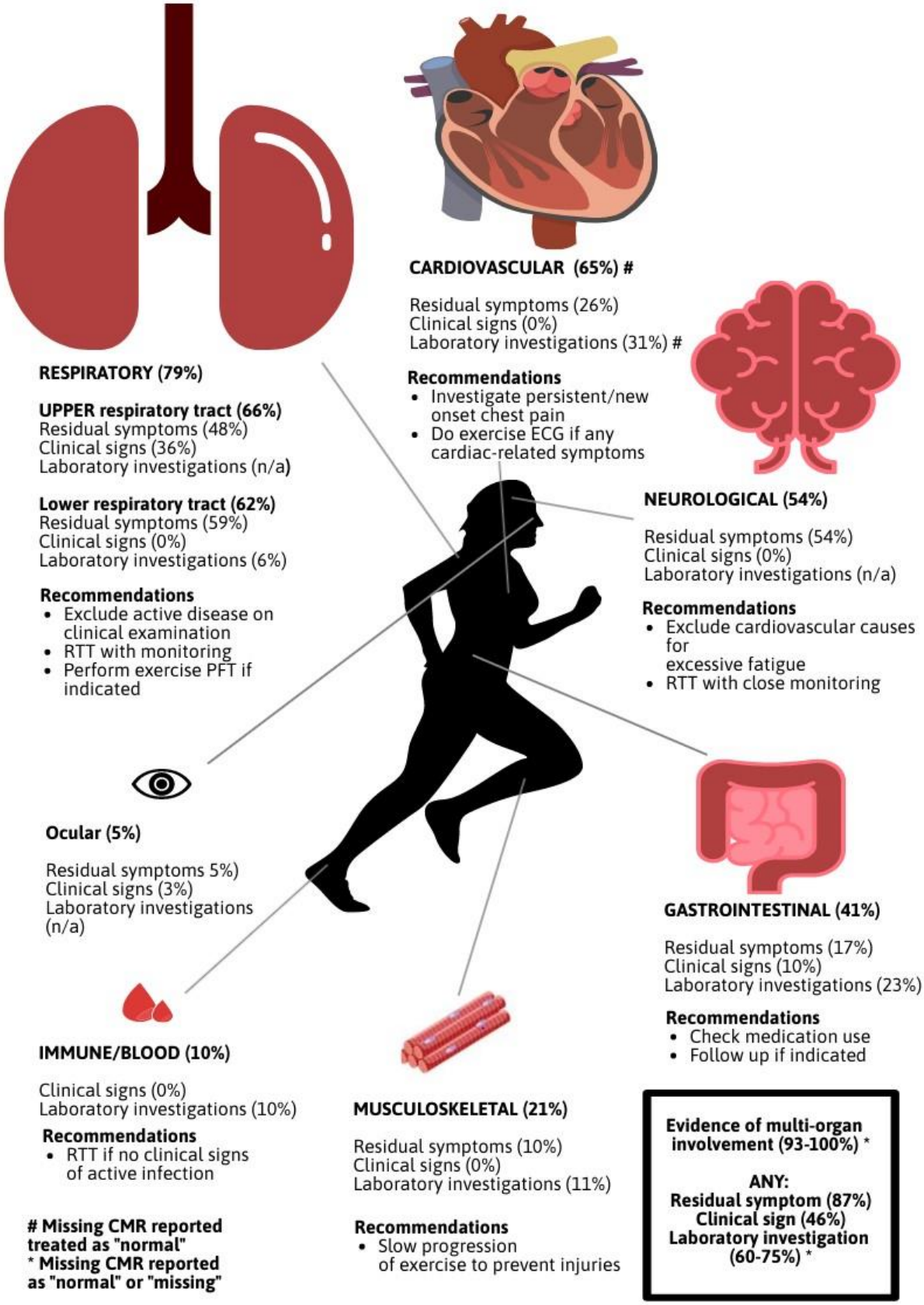

Figure 2: Multi-organ involvement in athletes with recent SARS-CoV-2 infection

In athletes assessed 10-28 days after onset of SARS-CoV-2 infection, the three organ systems with more frequent residual symptoms were the respiratory (upper and lower), neurological and cardiovascular systems. The high frequency of residual upper respiratory symptoms and positive clinical signs is expected, as SARS-CoV-2 is primarily a respiratory infection with predominant upper respiratory involvement. The frequency of residual lower respiratory symptoms was also high, but the clinical examination was normal in all cases and PFT's at rest were only abnormal in 6% of athletes. In athletes with residual neurological and cardiovascular symptoms, clinical examinations were all normal. We concluded that although residual symptoms are frequently reported in athletes assessed 10-28 days after acute SARS-CoV-2 infection, the yield on physical examination and laboratory investigations are low for these organ systems.

In exploring abnormalities in laboratory investigations, the 'cardiac triad' had a low yield of abnormalities; resting ECG (2%), ECHO (3%) and hs-cTnT (0%). This was similar to a study in which 2820 athletes underwent ≥1 element of cardiac triad screening with a yield of <1% abnormalities.[20] Although the 'cardiac triad' has been widely used as a screening tool for cardiac pathology,[18 36 37] the reliability of ECHO[18 38] and elevated hs-cTnT[39 40] to diagnose SARS-CoV-2-specific cardiac involvement, has been questioned. Our data highlight the importance of performing an exercise ECG, with a >3-fold increase in revealing abnormalities compared with a resting ECG. Exercise ECG testing was also advised by other authors[40-42] and should be considered if clinically indicated. In our study, myocarditis, as defined by the modified by Lake Louise criteria,[33] was diagnosed in only 1 athlete (1.5% of participants with CMR). This frequency of CMR-diagnosed myocarditis in athletes after SARS-CoV-2, is in keeping with a frequency of 0-5% that is reported in several studies[19 36 43] and confirmed in a recent systematic review.[44] We also observed a frequency of 31% of other cardiac abnormalities in 65 participants that underwent CMR, but this findings should be interpreted with caution because the clinical significance of these abnormalities is debated in the literature.[40] It has been shown that the presence of CMR abnormalities increases 4.2 fold when CMR is done when clinically indicated, compared to CMR done as routine screening of all athletes with SARS-CoV-2 infection.[20] We support the recommendation that CMR should be reserved for athletes with abnormal pathological findings,[45] persistent/new cardiopulmonary symptoms,[34] or unexplained exercise intolerance.[29]

The relatively high frequency of raised ALT/AST (about 15%) we show should also be interpreted with caution. Most of these values were only slightly elevated and could also be attributed to other causes such as the effect of medication used during the acute phase of infection. In addition, most athletes with raised CK levels (11%), had marginally elevated levels, and none had musculoskeletal symptoms. We recommend monitoring for symptoms and signs of rhabdomyolysis after exercise in athletes with modestly raised CK values.

The final and main novel aspect to our study was that we show that increased total number of acute symptoms in athletes with recent SARS-CoV-2 infection is related to multi-organ involvement (greater frequency and number of organs involved). These data are the first to provide evidence in support of the IOC Consensus recommendation[8] that fewer acute symptom (<5 symptoms) indicates mild illness with a lower risk of multi-organ involvement. Conversely, >10 acute symptoms are associated with increased frequency and number of organs involved, thus more severe illness. Therefore, the greater number of symptoms during the acute phase of SARS-CoV-2 infection, the greater the risk of multi-organ involvement. A recent AWARE study[13] showed that the number of symptoms during the acute infection phase is associated with prolonged RTT, thus increased time loss, which is an indicator of more severe illness in athletes.[6] In the general population, recent studies also report that ≥5 acute symptoms is associated with higher risk of prolonged duration of symptoms with a history of SARS-CoV-2 infection.[11 12] Factors influencing return to full sport performance and prolonged symptoms in athletes with SARS-CoV-2 infection, including total number of acute symptoms, require further investigation.

Practical clinical implications of this study

The findings of this study, support the recommendation in the IOC Consensus[8] that the first step in the RTS decision is to assess severity of ARinf. We recommend using the number of acute symptoms as an indicator of severity. Other clinically relevant messages for the SEM physician assessing athletes 10-28 days after acute SARS-CoV-2 infection are:

- Residual symptoms are common, especially in those athletes with a greater number of acute symptoms.
- The most common residual symptoms are: lower respiratory tract (shortness of breath, dry cough, chest tightness and dyspnoea), upper respiratory (blocked nose and sinus pressure), neurological (excessive fatigue and headache) and cardiovascular symptoms

(racing heart). In most cases, physical examination is normal, and abnormal laboratory investigations are more common if CMR is performed routinely. The clinical importance of individual CMR findings is yet to be determined.

- The high prevalence of lower respiratory symptoms should alert the SEM to possible exacerbation of underlying respiratory disorders e.g. asthma. This condition is commonly underdiagnosed in athletes[46 47] and should be considered if respiratory symptoms persists.
- The frequency and number of organ systems involved is significantly higher in athletes with greater number of symptoms during the acute phase of the infection.
- In athletes presenting with >5 acute symptoms, individualised laboratory investigations, based on symptoms and signs of suspected pathology, may be of value to assess for multi-organ system involvement
- Increased number of acute phase symptoms can serve as an indicator of illness severity

We recommend that the SEM follow the IOC consensus guidelines on RTS[8] with an individualised approach. Evidence of multi-organ involvement, based on symptoms only, is not necessarily a contra-indication to RTT. However, closer monitoring should be implemented once athletes return to training, specifically to monitor for the resolution of symptoms, normalisation of abnormal laboratory findings and to ensure normal adaptation to training until return to full performance.

Limitations

All clinical assessments were standardised and were performed in one clinic, by the same personnel, thus minimising inter-person interpretation differences. However, this study has several limitations. Firstly, the reporting of residual symptoms is subjective. Secondly, findings could not be compared to age-matched, non-infected controls and abnormal clinical and laboratory findings could not be attributed solely to recent SARS-CoV-2 infection (cause-effect). Pre-infection baseline testing was not feasible. Thirdly, our study population was self-selected and findings on frequency of multi-organ involvement cannot be generalised to all athletes with SARS-CoV-2 infection. For example, our study did not include athletes <18-years. Future studies on vaccinated athletes, different SARS-CoV-2 variants or other pathogens causing ARinf are needed for comparison. Additionally, we could only perform CMR on 68% of our study participants. Therefore, in the reporting of frequency of organ involvement (Table 1), we included both the upper and lower bound values if missing CMR data was assumed to be “normal” or “missing”. In the analysis where we

compared subgroups 1, 2 and 3, we did perform an additional analysis on only the subgroup of 65 participants with CMR, to determine if the relationship between subgroups by acute symptoms (frequency and number of organs involved) held, and found that this analysis confirmed our main finding. Finally, we recognise that small sample size was a limitation, specifically when comparing subgroups by organ systems.

How this study may affect research

We show that the total number of symptoms at the time of acute SARS-CoV-2 infection in athletes is associated with greater frequency multi-organ and greater number of organ systems involved. This is in keeping with results from a previous study reporting that greater number of acute symptoms is associated with prolonged return to training.[13] Future studies should explore: 1) the effect of SARS-CoV-2 vaccination on RTFP, 2) if greater number of symptoms during the acute phase of infection are related to time to return to pre-infection level of full sports performance, and 3) if the relationship between total number of symptoms during the acute phase of infection and RTFP also holds for non-SARS-CoV-2 pathogens. We recommend a standardised approach for the clinical reporting and assessment of ARinf (including SARS-CoV-2) in athletes so that research findings can be compared.

Supplementary material

Supplementary File A: Standardized clinical assessment of an athlete with acute respiratory infection

Supplementary Table A: Demographics, sport participation and history of co-morbidities for study participants (n=95)

Supplementary Table B: The frequency (% athlete assessments) of multi-organ involvement (residual symptoms or abnormal clinical signs/laboratory investigations) among athletes assessed 10-28 days after acute SARS-CoV-2 infection (individual variables)

Supplementary Table C: The frequency (% athlete assessments) of residual symptoms, abnormal clinical signs/laboratory investigations and cardiac magnetic resonance imaging for participants in three different subgroups based on total number of symptoms during the acute phase of the infection (individual variables)

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Competing interests

The authors have no competing interest to declare

Contributorship

Conceptualisation: CS, MS, KK. Methodology: CS, MS, MD, EJ. Writing and original draft: CS, MS. Interpretation of special investigations: LS, ADP, MM. Writing, reviewing, and editing: CS, MS, KK, MD, EJ, LS, ADP, MM. ECG and PFT testing performed: KK

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After the medical assessment for severity and multi-organ involvement of a recent SARS-CoV-2 infection (Chapter 6), the sport exercise and medicine physician can give advice on clearance to resume exercise, or to refrain from training until symptoms of concern have resolved or been investigated. Once training is resumed (RTT), the athlete then progressively increases training load until pre-infection level of full sports performance is achieved i.e. return to full performance (RTFP). This is the final time point in the RTS continuum. An athlete should continuously be monitored during the RTS process, as new symptoms may develop, or residual symptoms may persist.

Duration (days) to RTFP can be prolonged, and factors associated with prolonged RTFP, have to date, not been described in the literature. Chapter 7 addressed this knowledge gap by determining the days to RTFP, and explored the possible association with selected factors with prolonged RTFP.

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CHAPTER 7: Manuscript information

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Increased number of symptoms during the acute phase of SARS-CoV-2 infection in athletes is associated with prolonged time to return to full sports performance – AWARE VIII

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CHAPTER 7

Increased number of symptoms during the acute phase of SARS-CoV-2 infection in athletes is associated with prolonged time to return to full sports performance – AWARE VIII

7.1 ABSTRACT

Objective

The study aims to identify factors associated with prolonged time to return to full performance (RTFP) in athletes with recent SARS-CoV-2 infection.

Methods

Prospective cohort study with cross-sectional analysis. Eighty-four athletes with confirmed SARS-CoV-2 infection assessed at a COVID-19 recovery clinic gave a history of: age, sex, type/level of sport, co-morbidities, pre-infection training hours and 26 acute SARS-CoV-2 symptoms from three categories ("nose and throat", "chest and neck", "whole body"). Data on days to RTFP were obtained by structured interviews. Factors associated with RTFP were: demographics, sport participation, history of co-morbidities, pre-infection training history, acute symptoms (type, number). Outcomes were: 1) days to RTFP [median (interquartile range-IQR)] in asymptomatic (n=7) and symptomatic athletes (n=77), and 2) hazard ratios (HR; 95%CI) for athletes with vs. without a factor (univariate, multiple models). HR<1 was predictive of higher % chance of prolonged RTFP. Significance was $p<0.05$.

Results

Days to RTFP were 30 (23-40) for asymptomatic and 64 (42-91) for symptomatic participants (p=0.026). Factors associated with prolonged RTFP (univariate models) were: females (HR=0.57; p=0.014), endurance athletes (HR=0.41; p<0.0001), co-morbidity number (HR=0.75; p=0.001), respiratory disease history (HR=0.54; p=0.026). In symptomatic athletes, prolonged RTFP (multiple models that included significant co-variates) was significantly associated with increased total number of "all symptoms" (HR 0.91; p=0.001), "whole body" (HR=0.82; p=0.007), "chest and neck" (HR=0.85; p=0.017) and "nose and throat" (HR 0.84); p=0.013) symptoms.

Conclusion

Larger number of total symptoms and specifically "whole body" symptoms during acute phase of SARS-CoV-2 infection in athletes, is associated with prolonged RTFP.

7.2 INTRODUCTION

The potential burden of SARS-CoV-2 infection on athlete's health, especially the cardiopulmonary systems, has been investigated.[1-7] The impact of acute respiratory illness (ARill) including SARS-CoV-2 on the short and longer-term exercise and sports performance parameters was explored in a recent systematic review.[8] Despite the heterogeneity in the results of the reviewed studies, there was a trend towards impairment in both exercise and sports performance outcomes in athletes after a recent acute respiratory infection (ARinf). Specifically, a reduction in sports performance (self-reported training ability and capacity as well as overall training load) was observed in the post-ARinf period.[8]

The period of inability to train or compete after injury or illness is "time loss".[9] After a period of time loss, the process to return to sport (RTS) is a continuum rather than a single defined end point. This continuum has been described for injuries[10] but also holds for RTS after ARinf. The RTS process timeline after ARinf has two defined time points. The first time point is when an athlete resumes or starts training – days to return to training (RTT). An athlete then progressively increases training load until the final endpoint is reached when the athlete reaches pre-infection levels of sports performance, i.e. days to return to full performance (RTFP).

The days to RTT after an ARinf, and possible factors that are associated with days to RTT, have been explored in three studies.[11] [12] [13] Symptom clusters[11] or symptoms confined to the lower respiratory tract[12] were associated with prolonged RTT. More recently, reduced training in the 7 days before the infection and number of symptoms during the acute phase of infection, were predictive of prolonged RTT.[13] Data on days to RTT and associated factors are limited, however, no data are available on the time course (days) or associated factors on RTFP after a recent SARS-CoV-2 or other ARinf.

Therefore, the aim of this study was to report the number of days from the onset of symptoms/positive test to RTFP, and to identify factors associated with a prolonged time (days) to RTFP in a cohort of athletes with a recent SARS-CoV-2 infection.

7.3 METHODS

Study Design and Setting

This was a descriptive cross-sectional analysis of data collected in a prospective cohort study, which is part of the multi-centred Athletes With Acute Respiratory InfEctions (AWARE) research program conducted by the Sport, Exercise Medicine and Lifestyle Institute (SEMLI) at the University of Pretoria in South Africa. The most predominant SARS-CoV-2 variants during the recruitment phase, were the Ancestral virus and Beta and Delta variants and varying degrees of restrictions on human movement and sporting events were in place. Vaccination only became available in South Africa in a phased roll out in early 2021 and was not readily available to most participants. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria for the project (REC 409/2020 and REC 751/2019).

Participants and data collection

Participants were deemed eligible if they: 1) were athletes aged 18-60 years, 2) training >3 hours a week, 3) had a recent SARS-CoV-2 infection confirmed by Polymerase Chain Reaction (PCR) or antigen testing, 4) completed the online questionnaire, and 5) consented to partake in the study. Data collection was in two phases.

Data collection: Phase 1

The first phase of the study was a 15-month period, from 1 July 2020 to 30 September 2021. During this period, 105 participants were recruited and clinically assessed in SEMLI's 'COVID-19 recovery clinic' before exercise was resumed. Participants were followed up clinically over a period of four months. Participants completed an online questionnaire[11] hosted on the Research Electronic Data Capture (REDCap) platform,[14] containing the following sections: 1) demographics (age and sex), 2) sport participation (level/type of sport),[15] 3) history of co-morbidities, 4) 26 symptoms during the acute phase of SARS-CoV-2 infection (presence, number, duration and severity) per anatomical region "nose and throat", "chest and neck" and "whole body"/systemic, and 5) training history (hours of training 0 to 35 days before onset of infection). The total number of participants for phase 1 of the study was 105.

Data collection: Phase 2

In the follow-up period, 11 participants could not be contacted (supplementary figure 1). The remaining 94 participants were interviewed by a structured in-person or telephonic interview (January and March 2022). They were asked to report the days to RTT and RTFP as follows: 1) "*on which day was your first training session"* and 2) "*on which day were you back to you pre-COVID-19 sports performance level*?" Subsequently, they were asked if they had: "*no symptoms or health concerns but other factors prevented you from the first training session to return to the pre-illness level of performance e.g. work/travel/training venue access restrictions".* If the answer was 'yes' to this question, their data were excluded from the analysis, as the factors influencing RTFP were not considered to be SARS-CoV-2 related. A total of ten participants reported that factors such as work/travel/training venue access restrictions affected days to RTFP and they were excluded from the analysis. The number of remaining participants was 84. Two participants had a re-infection of SARS-CoV-2 (2 and 12 months after the initial infection). Data from both assessments were included, however demographic information was not duplicated. A total of seven participants were asymptomatic. In data analysis exploring symptoms during the acute phase of infection as factors influencing time to RTFP, these seven participants were thus excluded. For all analyses related to symptoms, only 79 assessments were included (supplementary figure 1).

Patient and public involvement

Athletes with a recent ARinf and medical practitioners involved in athletes' treatment, provided feedback on the questionnaire during the developmental stages.

Equity, diversity, and inclusion statement

Our research team consisted of four female and one male authors from 2 countries in Southern Africa (global south) representing three different sub-specialities within health care and biostatistics. The study population included peoples of all ethnicities, genders, and demographic/socio-economic backgrounds. We recognise that our data did not explore the impact of ethnicity and socio-economic backgrounds on the results.

Measures of outcome

The main aim was to identify factors associated with a prolonged time (days) to RTFP in a cohort of athletes with a recent SARS-CoV-2 infection. Specific factors include the following: demographics (age and sex), sport participation (level and type of sport), history

of number and type of co-morbidities, pre-infection training history and the presence and number of symptoms during the acute phase of infection. The days (median; IQR) from the onset of symptoms to RTFP as well as symptom characteristics [number (%), duration (days) (median; IQR) and severity (mild vs. moderate/severe)] by anatomical region are also reported.

Statistical analysis of data

Demographics, sport participation and history of co-morbidities in participants were described using n (%) or mean (SD) for all participants (n=84) and the symptomatic participants (n=77). The number of asymptomatic (n=7) participants was too small to report the full details on demographics, sport participation and history of co-morbidities. Two participants had a re-infection, thus 79 assessments on symptomatic participants and their pre-infection training history were described. The responses to the 26 SARS-CoV-2 symptoms (8 “nose and throat”, 8 “chest and neck” and 10 “whole body”) were described as: 1) the presence of symptoms [number of athletes (n, %)], 2) the duration in days (median; IQR) and 3) the severity [number (%) of mild and moderate/severe]. Days to RTT and RTFP were reported as median (IQR) for symptomatic and asymptomatic participant assessments but return to full performance (RTFP) analyses were performed on only the symptomatic participant assessments (n=79). One participant did not RTFP during the study period and was censored in the analysis.

Cox regression was used to model the factors associated with RTFP. Hazard ratios (HR; 95%CI) were reported with Chi-Square (p-values) (type 3 test) for significance ($p<0.05$) for: demographics, sport participation, history of co-morbidities and pre-infection training for symptomatic participant assessments (n=79) and 26 SARS-CoV-2 symptoms [individual and by anatomical region (“nose and throat”, “chest and neck”, “whole body” and “all symptoms”)]. Four multiple regression models for factors associated with RTFP were done for each anatomical region. Significant variables with $p<0.01$, were included in the initial models. A stepwise approach was used to configure the final multiple models. All models were adjusted for type of sport and return to training days (RTT.) The Hazard Ratio (HR; 95%CI) was reported with Chi-Square (p-values) (type 3 test) for significance ($p<0.05$).

7.4 RESULTS

Demographics, sport participation, history of co-morbidities and pre-infection training

The demographics, sport participation/type, history on co-morbidities and pre-infection training history of all participants (n=84) and the symptomatic (n=77) participants are shown in Table 1. The asymptomatic group consisted of six males (85%), a mean age of 20 years and a mean BMI of 25. All 7 asymptomatic participants competed in mixed sports and 3 (43%) were professional athletes.

Table 1: Demographics, sport participation, history of co-morbidities and pre-infection training of all study participants (n=84), and symptomatic participants (n=77)

Variable	**All participants (n=84)**	**Symptomatic participants (n=77)** [β]
Demographics		
Age (mean, SD)	24.5 (6.9)	24.8 (7.1)
Male sex (n, %)	53 (63.1)	47 (61.0)
Body mass index (kg/m^2)	24.4 (3.9)	23. 9 (3.8)
Sport participation		
Level of sport participation		
Professional sports (n, %)	42 (50.0)	39 (50.6)
Amateurs (n, %)	42 (50.0)	38 (49.4)
Type of sport		
Endurance (n, %)	38 (45.8)	38 (50.0)
Mixed (including skills n=1 and power n=1) (n, %)	45 (54.2)	38 (50.0)
History of co-morbidities		
Number of co-morbidities per participant (mean, SD)	0.8 (1.0)	0.8 (1.0)
Any co-morbidity (yes) (n, %)	44 (52.4)	39 (50.7)
Respiratory	25 (29.8)	23 (29.9)
Asthma	17 (20.2)	15 (19.5)
Cardiovascular disease	8 (9.5)	7 (9.1)
Gastrointestinal	9 (10.7)	8 (10.4)
Nervous system	10 (11.9)	8 (10.4)
Allergies (yes) (n,%)	23 (27.4)	23 (29.9)
Pre-infection training history #	**All participant assessments (n=86)**	**Symptomatic participant assessments (n=79)** [#]
Training 7 days prior to onset of symptoms (hrs/week) (mean, SD)	9.1 (6.8)	9.2 (6.8)
Weekly training 2-5 weeks prior to onset of symptoms (hrs/week) (mean, SD)	12.99 (8.6)	12.9 (8.7)
Days to return to training (RTT) (mean, SD)	19 (12.4)	19.5 (12.8)

[β] Symptomatic participants (without duplications of re-infection) n=77
Data on two symptomatic participants with re-infection are included
RTT, return to training
Missing data on participants: a=1

The study population (n=84) had a mean age of 25 years, the majority were males (63%) and 50% were professional and 46% were endurance athletes. A history of co-morbidity was reported by 52%, respiratory disease (30%), asthma (20%) and allergies by 27% of all participants. Six (7%) of all the study participants were vaccinated. The demographics of the symptomatic participants were very similar to all participants, although slightly more reported allergies (2.5% more) and more were endurance athletes (4.2% more).

Time course (days) from onset of symptoms to RTFP

Symptomatic and asymptomatic participant subgroups

For asymptomatic participants (n=7), the median days from the positive SARS-CoV-2 test to RTT was 13 days (IQR: 11-24), and days to RTFP was 30 (IQR: 23-40) (supplementary figure 2). The median days from RTT to RTFP was 14 days (IQR: 7-22). For symptomatic participants (n=79), the median days for onset of symptoms of SARS-CoV-2 infection to RTT was 16 days (IQR: 12-24) with a maximum of 90 days. The median days for onset of symptoms to RTFP was 64 days (IQR: 42-91), with a maximum of 415 days. In evaluating the time course (days) from RTT to RTFP in the symptomatic participants, the median was 44 days (IQR: 21-75).

The days to RTFP for symptomatic participants (median=64; 95%CI:53-75) was significantly longer compared with asymptomatic participants (median=30; 95%CI: 18-40) (p=0.026). As symptoms seem to play an important role in the timeline to RTFP all subsequent analyses were performed on the symptomatic participant assessments.

Characteristics of symptoms of SARS-CoV-2 infection per anatomical region during the acute phase of infection in the symptomatic subgroup assessments (n=79)

The presence [number (%)], duration (median: IQR) and severity [n (%) of mild and moderate/severe] of symptoms during the acute phase of infection for the 79 participant assessments are summarised in supplementary table A. The mean (SD) number of symptoms per assessment for all anatomical regions was 8.3 (4.5) and for each anatomical region was: “nose and throat” 3.4 (1.8), “chest and neck” 2.4 (1.8), and “whole body” 2.6 (1.9). Symptoms in the “nose and throat” region were reported by 79 (100%) participants, 68 (86%) indicated they had at least one symptom in the “chest and neck” region and 63 (80%) had “whole body’ (systemic) symptoms. The most common specific symptoms were blocked

nose (66%), excessive fatigue (62%), sore/scratchy throat and headache (both 60%), and altered/loss of sense of smell (57%) or taste (51%).

Reported symptoms with a duration of 7 or more days were excessive fatigue, altered/loss sense of taste, altered/loss sense of smell and dry cough. The most common moderate/severe symptoms were excessive fatigue (53%), altered/loss sense of smell (46%) and headache (43%).

Factors associated with the time course from onset of symptoms to RTFP (univariate models)

RTFP and demographics, sport participation/type, history of co-morbidities, and pre-infection training history (univariate model)

The Hazard Ratio (HR and 95%CI) for the association between time to RTFP and demographics, sport participation and history of co-morbidities for symptomatic participants (n=77) is shown in Table 2. Pre-illness training history and days RTT is shown for 79 participant assessments because 2 participants had re-infections thus two assessments each (n=79 assessments). A HR<1 indicates a higher chance (%) of prolonged RTFP after the onset of the infection.

Table 2: The Hazard Ratio (95%CI) for return to full performance (RTFP) by demographics, sport participation, history of co-morbidities and pre-infection training history as possible factors associated with time to return to full performance (RTFP) for symptomatic participants (n=77) (Univariate model)

Variable	Symptomatic participants (n=77)		
	Hazard ratio [#] 95%CI	Chi-square	p-value
Demographics			
Age (years) [¤]	0.98 (0.95-1.01)	2.10	0.148
Females (vs. males)	0.57 (0.37-0.89)	6.03	**0.014**
Body mass index (kg/m^2) [¤]	1.10 (1.0-1.14)	3.80	0.051
Sport participation			
Level of sport participation			
Professional (vs. amateur)	0.65 (0.41-1.03)	3.42	0.065
Type of sport			
Endurance (vs. mixed)	0.41 (0.28-0.60)	21.19	**<0.0001**
History of co-morbidities			
Number of co-morbidities per participant [¤]	0.75 (0.6-0.93)	6.72	**0.001**
Any co-morbidity (yes vs. no)	0.64 (0.42-1.0)	3.89	**0.049**
Respiratory (yes vs no) [µ]	0.54 (0.31-0.93)	4.93	**0.026**
Allergies (yes vs no)	0.63 (0.38-1.03)	3.44	0.064
Pre-infection training history	**Symptomatic participant assessments (n=79)** [^]		
Training 7 days prior to onset of symptoms (hrs/week) [¤]	1.02 (0.99-1.05)	1.64	0.201
Weekly training 2-5 weeks prior to onset of symptoms (hrs/week) [¤]	1.02 (1.0-1.04)	2.66	0.103
Days to return to training (RTT) [¤]	0.97 (0.95-0.99)	7.38	**0.007**

[#] Ratio of the hazard of an individual with the co-variate compared to the reference factor
[¤] Continuous variables
[µ] Numbers on other co-morbidities including cardiovascular, gastrointestinal and nervous system, were too few to calculate HR
[^] Training history is reported for 79 assessments (2 athletes had re-infections)

Demographic factors associated with prolonged time to RTFP for symptomatic participants were: female sex (p=0.014), endurance sport (p<0.0001), number of co-morbidities (p=0.001), history of a respiratory disease (p=0.026) and days to RTT (p=0.007).

RTFP and presence of symptoms by anatomical region and specific symptoms (univariate model)

The Hazard Ratio (HR and 95%CI) for the association between time to RTFP and the presence of symptoms by anatomical region, and specific symptoms during the acute infection is shown in supplementary table B.

Significant associations between presence of symptoms by anatomical region and prolonged RTFP (% higher chance) is as follows: any "chest and neck" symptoms (65%; p=0.0005) and any "whole body" symptoms (60%; p=0.004). Specific symptoms most commonly associated with prolonged RTFP (% higher chance) by anatomical region were: 1) "whole body" region: excessive fatigue (68%; p<0.0001), loss of appetite (51%; p=0.006), nausea (46%; p=0.030), fever (45%; p=0.013), chills (45%; p=0.017), general muscle aches (43%; p=0.014), and 2) "chest and neck" region: chest pain/pressure (47%; p=0.006), headache (46%; p=0.010) and chest tightness (44%; p=0.032). None of the "nose and throat" symptoms were associated with prolonged RTFP.

RTFP and number of symptoms per anatomical region during acute phase of infection (univariate model)

The Hazard Ratio (HR and 95%CI) for the association between time to RTFP and the number of symptoms during the acute infection by anatomical region is shown in Table 3.

Table 3: The Hazard Ratio (95%CI) for return to full performance (RTFP) and number of symptoms during the acute phase of infection by anatomical region for symptomatic participant assessments (n=79) (Univariate model)

Number of symptoms by anatomical region	Q1;median;Q3	Hazard Ratio (95%CI) [#]	Chi-Square	p-value
Number of symptoms [φ]				
Nose and Throat	2;3:4	0.85 (0.73-0.98)	5.04	**0.025**
Chest and Neck	1;2;3	0.79 (0.72-0.87)	22.79	**<0.0001**
Whole Body	1;2:4	0.74 (0.65-0.83)	23.37	**<0.0001**
All symptoms	5;8;11	0.88 (0.83-0.92)	26.00	**<0.0001**

[#] Hazard Ratio of the hazard of RTFP for an individual with an increased number of symptoms in each anatomical region HR<1 indicates a higher chance of RTFP after the onset of infection

[φ] For number of symptoms, the hazard ratio indicates the change in the risk for 1 more symptom

The association between number of symptoms by anatomical region and prolonged RTFP (% higher chance) is as follows: "nose and throat" (15%; p=0.025), "chest and neck" (21%; p<0.0001), "whole body" (26%; p<0.0001) and all symptoms (12%; p<0.0001).

Factors associated with the time course from onset of symptoms to RTFP after recent SARS-CoV-2 infection (multiple models)

In the multiple models, significant covariates with p<0.01 (type of sport, number of co-morbidities and number of days to return to training) were included. Only type of sport and days to return to training remained significant. Therefore, in the multiple models we adjusted for type of sport and days to return to training. The adjusted Hazard Ratios (HR and 95%CI)

for number of symptoms per anatomical region, as well as total number of all symptoms, associated with RTFP, are reported in Table 4.

Table 4: The Hazard Ratio (95%CI) for return to full performance (RTFP) and number of symptoms during acute phase of infection by anatomical region (adjusted for type of sport and days to return to training) for symptomatic participant assessments (n=79) (Multiple models)

Number of symptoms by anatomical region	Q1;median;Q3	Hazard Ratio (95%CI) [#]	Chi-Square	p-value
Number of symptoms				
Nose and Throat	2;3:4	0.84 (0.74-0.97)	6.14	**0.013**
Chest and Neck	1;2;3	0.85 (0.74-0.97)	5.70	**0.017**
Whole Body	1;2:4	0.82 (0.70-0.95)	7.28	**0.007**
All symptoms	5;8;11	0.91 (0.86-0.96)	10.55	**0.001**

[#] Hazard Ratio of the hazard of RTFP for an individual with an increased number of symptoms in each anatomical region HR<1 indicates a higher chance of prolonged RTFP after the onset of infection

In the multiple models, prolonged time to RTFP (higher % chance) was significantly associated with an increase in the number of symptoms in each of the anatomical regions: “nose and throat” (16%; p=0.013); “chest and neck” (15%; p=0.017), “whole body” (18%: p=0.007) and “all symptoms” (9%; p=0.001). The relationship between days from the onset of symptoms to RTFP (horizontal axis) and the probability of survival (not RTFP) (vertical axis) for ‘total acute symptoms’ at Q1 (5 symptoms), median (8 symptoms), and Q3 (11 symptoms) is shown in Figure 1.

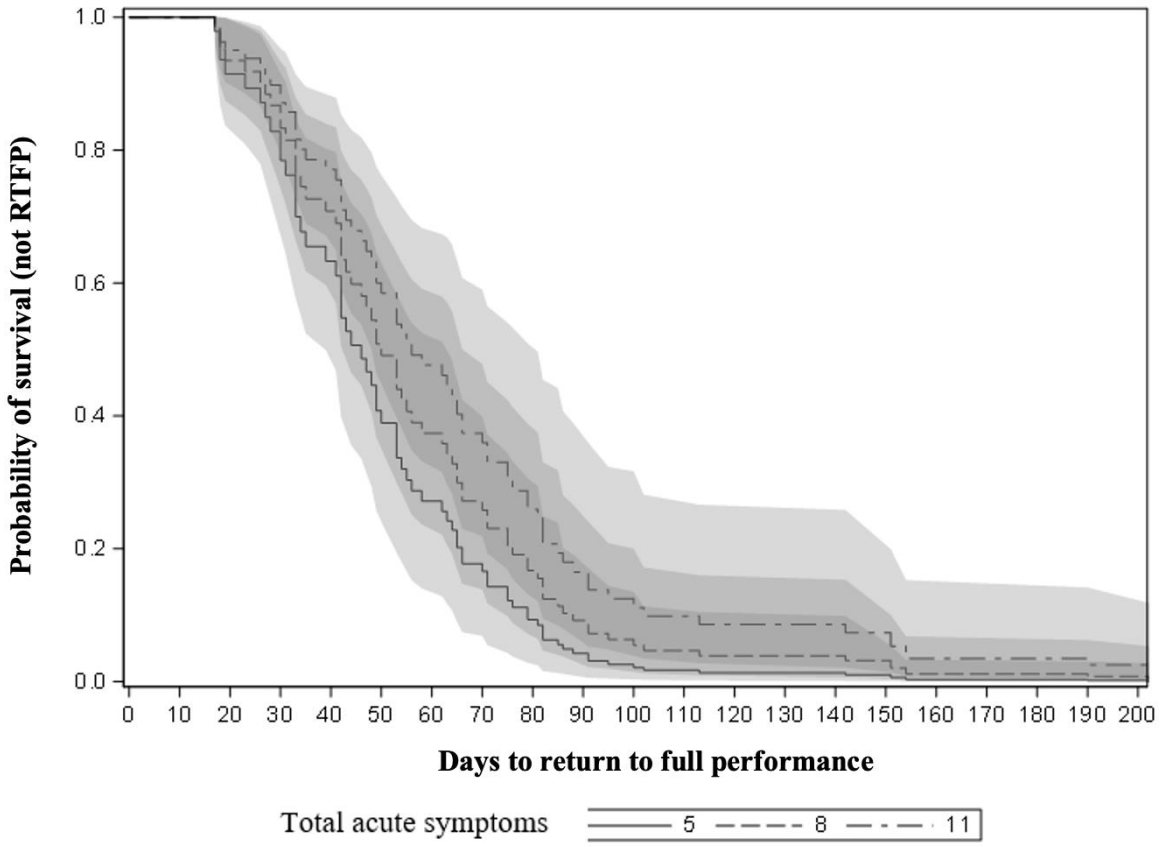

Figure 1: The relationship between days from the onset of symptoms to RTFP (horizontal axis) and the probability of survival (not RTFP) (vertical axis) for 'total acute symptoms' at Q1 (5 symptoms), median (8 symptoms), and Q3 (11 symptoms) (shaded areas are 95%CIs)

7.5 DISCUSSION

The first main finding of this study was that the time from the onset of symptoms/positive test to RTFP was twice as long for symptomatic athletes vs. asymptomatic athletes (p=0.026). Symptoms during the acute phase of infection thus seemed to be an important factor determining time to RTFP. A second main finding was that, in univariate analyses, we identified several factors that are associated with prolonged RTFP in symptomatic participants. These factors were: females (p=0.014), endurance sport (p<0.0001), number of co-morbidities (p=0.001), history of respiratory disease (p=0.026), and days to return to training (p=0.007). The presence of symptoms by anatomical regions "whole body" (specifically excessive fatigue, loss of appetite, nausea, fever, chills, and general muscle aches) and "chest and neck" (chest pain/pressure, headache, and chest tightness) were also significantly associated with prolonged RTFP. Our third main finding was that we identified that the total number of symptoms and the number of symptoms per anatomical region

remained significantly associated with prolonged RTFP when adjusted for type of sport and days to return to training in multiple models.

To the best of our knowledge, there are no other data on both the time to RTFP, and factors that are associated with prolonged time to RTFP in athletes after ARinf. Days to RTT and factors associated with RTT in athletes after ARinf have been reported in a few studies.[11,12] Symptom clusters of mainly systemic ("whole body") or chest related-symptoms ("chest and neck") including excessive fatigue, fever, loss of appetite, altered/loss sense of smell, headache, chest pain/pressure and difficulty in breathing, were significantly associated with prolonged RTT.[11] In another study, dyspnoea, chest pain, cough and fever were associated with for prolonged time loss (relative risk of 2.1).[12] Our study shows that symptoms in these two anatomical regions also have a significant impact on prolonged RTFP.

Acute SARS-CoV-2 symptoms can persist after the initial infection.[16] In our study, residual respiratory symptoms, fatigue, headache and muscle pain were associated with prolonged time to RTFP. Athletes with persistent symptoms should be appropriately investigated and treatment should commence, where appropriate, so that these athletes can reach pre-infection level of performance sooner.

Total number of acute symptoms and number of acute symptoms in each anatomical region, have been associated with prolonged RTT.[13] Our study shows that these two parameters are also associated with prolonged RTFP. We have no data from other studies in athletes to compare our findings to, but we note, with interest, that studies in the general population showed that ≥ 5 acute symptoms is associated with a higher risk of prolonged duration of symptoms after SARS-CoV-2 infection.[17 18] These emerging data suggest that greater number of acute symptoms may indicate more severe COVID-19, resulting in prolonged recovery. We recognise that our findings need to be replicated in other populations, and with larger sample sizes.

From our univariate analysis we show that female athletes had longer duration to RTFP, and this finding is to some extent supported by data from two studies where females had greater number of acute SARS-CoV-2 symptoms[12] and female athletes had a longer period to RTT[13] compared to males. In the univariate analysis we also show that endurance athletes had prolonged RTFP. In one study, endurance athletes returned to training quicker[13] but the time

to reach the full pre-infection performance level was not reported. A prolonged adaptation to training, once training after SARS-CoV-2 infection in endurance athletes resumes, may be a reason for this observation, but this requires investigation.

Finally, in the univariate analysis we show that a history of co-morbidities, specifically respiratory co-morbidities (mostly asthma) were associated with prolonged RTFP. In the general population several co-morbidities have been associated with poorer clinical outcomes of SARS-CoV-2 infections.[19] We also show that the presence of dry cough and chest tightness were associated with prolonged RTFP. Therefore, at the time of the first clinical assessment, athletes with a history of underlying respiratory disease should be identified as being at higher risk for prolonged RTFP. Asthma is often underdiagnosed in the athletic population[21, 22] and should also be considered. We suggest that athletes' symptoms should be monitored once training resumes. New and persistent exertional symptoms should also be investigated appropriately.[16]

Limitations of the study

In our study, participants were self-selected and this limits the generalisability of our findings to other populations of athletes with SARS-CoV-2 infection. We also recognise that RTT and RTFP dates were self-reported. However, the data were collected during a structured interview by the principal investigator (CS) as part of following-up the cohort. Our population of athletes were interviewed during the COVID-19 pandemic, which was at a time when the significant impact of SARS-CoV-2 on the well-being and sport opportunities made athletes more aware of their performance and recovery. Data were collected during the dominance of specific SARS-CoV-2 variants and 93% of participants were unvaccinated and our findings may not apply to other variants and pathogens causing ARinf. Sports performance is multi-factorial and we acknowledge that the time to RTFP could not solely be attributed to the effects of SARS-CoV-2 infection. Other factors e.g. the psychological impact of the isolation during acute infection, fear and lack of motivation to train when competitions were limited during the pandemic, and other factors could all have influenced time to RTFP. Finally, our study design was cross-sectional, and although significant associations with prolonged RTFP was shown, these do not infer a cause-and-effect relationship.

Clinical implications

Knowledge of the expected time to RTFP as well as identifying factors associated with prolonged RTFP can assist the athlete, coach and medical staff in planning training schedules to reach set goals to return to full performance after an infection. For the medical staff attending to athletes with SARS-CoV-2 infection, increased number of acute symptoms as well as the presence of "whole body" and "chest and neck" symptoms, may indicate longer time to RTFP. Athletes presenting with more acute symptoms, and acute symptoms from these anatomical regions, warrant a detailed history, further investigations, appropriate management and closer monitoring once exercise resumes. Knowledge of the number of symptoms during the acute phase of SARS-CoV-2 infection, may also assist the sport and exercise medicine (SEM) physician with RTFP timelines.

7.6 CONCLUSION

Our study is novel, and as far as we are aware, it is the only study reporting the days to RTFP and factors affecting the time course to RTFP. Knowledge related to the time course to RTFP can assist in the planning for athletes to achieve peak performance at sporting events. Special attention should be given to the following athletes with SARS-CoV-2 infection: females, endurance athletes, athletes with co-morbidities (especially respiratory disease) and athletes presenting with many symptoms (>5) during the acute phase of infection. Athletes presenting with a history of acute symptoms in the "whole body" and "chest and neck" regions should be accurately documented and monitored once exercise resumes. Persistent symptoms may influence time to RTFP, and if athletes report these, they should be investigated and managed appropriately. Underlying co-morbidities should also be identified.

What is already known?

- SARS-CoV-2 may negatively impact sports performance
- Increased total number of symptoms, and increased number of symptoms per anatomical region are associated with prolonged RTT

What are the new findings?

- In athletes with SARS-CoV-2 infection, the time from onset of symptoms/positive test to RTFP is twice as long in symptomatic vs. asymptomatic athletes
- Female and endurance athletes with SARS-CoV-2 infection, and those with more co-morbidities and history of respiratory disease, may have a prolonged RTFP

- In athletes with SARS-CoV-2 infection, the presence of acute symptoms in both the "whole body" and "chest and neck" regions can prolong RTFP
- In athletes with SARS-CoV-2 infection, both the number of acute symptoms in each anatomical region and the total number of all acute symptoms, are associated with prolonged RTFP

How this study may affect research

Future studies are needed to determine time to RTFP and associated factors in larger cohorts of athletes, vaccinated athletes, other SARS-CoV-2 variants and non-SARS-CoV-2 ARinf. Research to determine factors influencing the time to RTT and RTFP after ARinf, are also suggested.

Contributorship

CS and NS: study planning, data collection, data interpretation, manuscript (first draft), manuscript editing

EJ and MD: data cleaning, data management, data analysis including statistical analysis, data interpretation, manuscript editing

MS: responsible for the overall content as guarantor, study concept, study planning, data collection, data interpretation, manuscript editing, facilitating funding

Competing interests

The authors have no competing interests to declare

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Supplementary material

Supplementary figures

Supplementary figure 1: Study participants and number of participant assessments

Supplementary figure 2: Duration days from onset of symptoms or positive test to RTT and RTFP

Supplementary tables

Supplementary table A: The number (%), duration (days) and severity (mild or moderate/severe) of specific symptoms and symptoms by anatomical region in all symptomatic assessments (n=79)

Supplementary table B: The Hazard Ratio (95%CI) for return to full performance (RTFP) and the presence of symptoms during the acute phase of infection by anatomical region and specific symptoms (n=79) (Univariate model)

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In Chapter 2 and Chapter 3 of this thesis, knowledge gaps in RTS parameters were identified. These knowledge gaps were addressed in the subsequent original research manuscripts as follows:

Firstly, the incidence of acute respiratory infections (ARinf) including SARS-CoV-2, was determined in Chapter 4. Secondly, the duration to return to training (RTT) and factors associated with prolonged RTT, were explored in Chapter 5. Thirdly, evidence of multi-organ involvement after a recent SARS-CoV-2 infection, was reported in Chapter 6. Finally, the duration (days) to RTFP and factors associated with prolonged RTFP were reported in Chapter 7. The main findings of these original research studies will be summarised and discussed in Chapter 8. Limitations were discussed in detail in each separate chapter, but will be summarised in the final discussion section of this thesis. Lastly and most importantly, these novel and clinically relevant findings will be translated into practical and medically directed RTS guidelines for the athlete with a recent SARS-CoV-2 infection.

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CHAPTER 8

SUMMARY AND CONCLUSION

8.1 INTRODUCTION

Acute respiratory infection (ARinf) is the most common acute illness affecting athletes.[1-5] After the first cases of SARS-CoV-2 infection were identified in December 2019, the COVID-19 pandemic contributed significantly to the health burden in the general population, and also in athletes. In the early phase of the COVID-19 pandemic, the focus was on reducing the transmission and impact of this virus, and this also applied to athletes as they returned to sport. Therefore, it was important to determine the incidence of SARS-CoV-2 infection in cohorts of athletes, identify associated risk factors related to transmission, and to implement risk mitigation strategies. In contact sports specifically, such as rugby, the risk of SARS-CoV-2 transmission was not known. This was a knowledge gap that is addressed in this thesis.

In the early phases of the COVID-19 pandemic, it became increasingly relevant that athletes with recent SARS-CoV-2 infection needed guidance on the safe return to sport (RTS) after infections. It is well known that ARinf can result in the unavailability to train and compete, i.e. 'time loss'.[6] The RTS after an injury is not a point in time but a process or continuum.[7] In the recently published IOC Consensus statement on acute respiratory infections in athletes,[8] this process was adapted for RTS after acute illness. Two time points in the RTS period were identified: 1) return to training (RTT), and 2) return to the pre-infection level of sport performance, i.e. return to full performance (RTFP). The sport and exercise medicine (SEM) physician needs to provide the athlete with safe RTS guidelines during this process, thereby mitigating possible medical complications.[9-12]

For the SEM to provide medical clearance for the first step in the process (RTT), the clinical presentation and effects of ARinf, need to be understood. At the onset of the COVID-19 pandemic there were no data to guide the SEM physician in the RTT or RTFP time points. Initial results from research studies, focused mainly on the cardiovascular system.[13-19] Studies in the general population, reported that SARS-CoV-2 infection can result in multi-organ involvement but there was limited knowledge on the multi-organ involvement of SARS-CoV-2 in athletes. This is important because the physiological stress of exercise is a multi-organ response. Multi-organ involvement after SARS-CoV-2 infection in athletes, was

identified as another area where more research was required. The time course (days) to RTT and RTFP after ARinf in athletes, as well as factors associated with these two time points, were also not available. RTT and RTFP time points were addressed in this thesis.

The study objectives of this thesis were set out in Chapter 1. These objectives focused on the knowledge gaps that were identified in the literature reviews (Chapters 2 and 3) and were address in the original research findings reported in Chapter 4, 5, 6 and 7.

8.2 SUMMARY OF THE MAIN RESEARCH FINDINGS

A summary of the main research findings of this thesis is as follows:

Systematic review and meta-analysis: Days to RTS, frequency of time loss illness and symptom duration of ARinf (suspected and confirmed) in athletes

In Chapter 2, a systematic review on the following RTS outcome variables is reported: 1) days to RTS, 2) frequency time loss and 3) symptom duration.[20] Only four studies recorded the actual days to RTS after an ARinf.[21-24] This period from onset of symptoms to RTS varied among studies, from 1.7±2.3 days[22] to 3.5±5.0 days.[24] In another study, no days were lost due to upper ARinf but lower infection resulted in up to 7 days lost[21] compared to 2.5 days lost per lower ARinf illness episode reported in the fourth study.[23] These studies did not identify the causative pathogen or defined the severity of disease.

The frequency of time loss infection was reported as 20% of ARinf. The mean symptom duration was seven days, regardless of the anatomical or pathological classification of ARinf or the method of diagnosis.[20] Again, in the majority of the studies, causative pathogens were not identified, and the duration of specific symptoms or symptoms by anatomical region was not reported. After the completion of this systematic review, the term 'return to training' (RTT) was adopted as the first clinical decision time point in the RTS continuum. Similar outcome variables were investigated for SARS-CoV-2 infection in athletes.

Narrative review: Recommended time (days) to RTT and screening protocols after SARS-CoV-2 infection

In March 2020, a global COVID-19 pandemic was declared.[25] The novelty of the SARS-CoV-2 virus caused great uncertainty on the RTT recommendations of athletes with a recent

infection. The global chaos that the pandemic caused, restrictions on sporting activities and fear of adverse medical outcomes for athlete resuming training, all had a potential impact on RTT guidance. Expert opinions on recommended days to RTT varied considerably and were reviewed and summarised in Chapter 3. Initially, fixed time periods were advocated, regardless of symptoms,[26 27] but later days to RTT were determined by the resolution of acute or cardiopulmonary symptoms.[28-34] In the early phases of the pandemic, screening protocols were mostly standardised for symptomatic infection (mild, moderate or severe)[28 29 35 36] but later testing was guided by symptoms,[37 38] suspicion of cardiovascular involvement[33] or abnormal physical findings.[30 32] Despite a vast number of expert opinions, original data on RTS parameters i.e. actual days to RTT and symptoms duration, as well as symptom number and factors associated with time to RTT, remained limited.

Data from original research on RTS outcomes were obtained from six studies. Actual recorded days to RTT ranged from a median of 17-30 days in three studies.[39-41] Symptom duration was found to be <7 days for elite football players,[42] and 9±14 (mean, SD) for competitive athletes.[43] In two more studies, symptom duration was 5.0 ± 3.9 to 7.5 ± 4.2 (mean, SD) in mixed elite athletes[44] and a median of ten days in a collegiate cohort.[40] The number of symptoms per athlete was reported in one study as 10.4.[41] Factors associated with RTT were symptom clusters (chest pain, excessive fatigue, chills, fever, headache, altered/loss sense of smell, chest pain/pressure, difficulty in breathing and loss of appetite),[41] symptoms confined to the lower respiratory tract,[40] and specific symptoms (chest pain).[40] Data on factors associated with prolonged RTT are therefore limited, while no data was available on RTFP time course or associated factors.

Original research study: Incidence (per 1000 player days) of ARinf, including SARS-CoV-2 in a cohort of athletes during different phases of lockdown during the COVID-19 pandemic

Before the impact of SARS-CoV-2 infection on athlete's health and ability to train could be determined, it was important to determine the incidence of SARS-CoV-2 and associated risk factors within a cohort of athletes engaged in contact sport, which has a potentially high risk of SARS-CoV-2 transmission. In this study, the incidence during four phases from complete lockdown to competition was reported in a cohort of 319 student rugby players. The return to competition after lockdown was divided in phases as follows: two non-contact (individual and non-contact team training), and two contact phases (contact team training and

competition). The incidence for ARinf over a 13-month period was 0.31 and that of SARS-CoV-2 was 0.23 per 1000 player days. The incidence of SARS-CoV-2 increased progressively from full lockdown to competition, with a significant higher incidence during contact phases (3 and 4) compared to non-contact phases (1 and 2) ($p<0.01$). In this study, symptom characteristics were similar in subgroups and factors including demographics, level of sport, co-morbidities, allergies, influenza vaccination, injuries and lifestyle habits were not associated with ARinf.

Original research study: Factors associated with prolonged RTT in athletes with recent SARS-CoV-2 infection

After a period of acute illness, athletes and coaches need to know when training can resume. Time (days) to RTT and factors that may be associated with prolonged RTT is thus important and this was explored in an original research study reported in Chapter 5. In a cohort of 207 athletes of mixed sport types, the median days to RTT were 14 (IQR;10-21) days and the mean number of symptoms during the acute phase of infection was 7.3.[45] Univariate and multiple models were used to determine if factors were associated with prolonged RTT. In the univariate analysis, females and less training in the seven days before infection, as well as regional ("neck and chest") or systemic symptoms ("whole body") were associated with prolonged RTT. In multiple models (adjusted for training in the seven days before infection), the total number of symptoms and number of symptoms in each anatomical region, remained significantly associated with prolonged RTT.

For an athlete to resume exercise (RTT), the severity of the infection should be determined to provide medical clearance, if indicated. More importantly, multi-organ involvement needs to be evaluated to provide safe RTT.

Original research study: Multi-organ involvement in athletes, assessed 10-28 days after onset of SARS-CoV-2 infection

In a prospective cohort study reported in Chapter 6, 95 athletes were assessed 10-28 days after a recent confirmed SARS-CoV-2 infection. Evidence of multi-organ involvement was found in 93-100% of athletes and included: residual symptoms (87%), clinical signs (46%), and laboratory investigations (60-75%). Athletes were divided into subgroups according to the number of symptoms during the acute phase of infection. Females and endurance athletes had more symptoms (>5) during the acute phase of infection. The most frequently reported

residual symptoms were lower respiratory (mainly shortness of breath and dry cough), upper respiratory (mostly blocked nose and sinus pressure), neurological (predominantly excessive fatigue and headache) and cardiovascular (especially racing heart). Athletes with >10 symptoms during the acute phase of infection, had significantly more residual respiratory (upper and lower) and neurological symptoms. Abnormal findings on physical examination and laboratory investigations, did not differ significantly between subgroups, but participant numbers were too few to compare some variables. The cardiac triad (resting ECG, ECHO, hs-cTnT) had a low yield of abnormalities and the use of elements of the triad for screening of all athletes, have been questioned.[18 46 47 48] A subset of participants (n=65) had cardiac magnetic resonance imaging (CMR). One participant (1.5%) was diagnosed with myocarditis based on the modified Lake Louise criteria.[49] Finally, the novel finding was that the total number of acute symptoms in athletes with recent SARS-CoV-2 infection is related to multi-organ involvement (greater frequency and number of organs involved). More specifically, more than five acute phase symptoms, were significantly associated with an increased number of organ involvement. Once an athlete resumes training (RTT), the main goal is to reach pre-infection level of full sports performance. Factors associated with return to full performance (RTFP) after SARS-CoV-2 infection in athletes have not been explored.

Original research study: Factors associated with prolonged RTFP in athletes with recent SARS-CoV-2 infection

After training resumes, the athlete aims to reach pre-infection level of sport performance, i.e. return to full performance, in the shortest possible duration. In an original research study (Chapter 7), a cohort of 84 athletes, aged between 18 and 60 years, were followed up over four months. Seven athletes were asymptomatic during the acute phase of infection and 77 reported acute symptoms. The days from positive test to RTT for the asymptomatic group was a median (IQR) of 13 (11-24), and time to RTFP was 30 (23-40) days. The symptomatic group had duration from onset of symptoms to RTT of 16 (12-24) days and RTFP of 64 (42-91) days. Days between RTT and RTFP was 14 (7-22) and 44 (21-75) for asymptomatic and symptomatic athletes respectively. RTFP was therefore twice as long for symptomatic athletes and differed significantly from the asymptomatic group (p=0.026). The impact of symptoms on RTFP timelines were emphasised. The mean number of symptoms were 8.3 (±4.5).

Factors associated with prolonged RTFP in a univariate analysis were females, endurance athletes, number of co-morbidities and history of respiratory disease. Further analyses

revealed the association between the presence of any "whole body" or "chest and neck" symptoms, and specifically excessive fatigue, loss of appetite, nausea, fever, chills and general muscle aches and prolonged RTFP. Although participants were from a large age range, age was not associated with time to RTFP. In multiple models, in increase in the number for each anatomical region as well as total number of symptoms, remained significant after adjustment for type of sport and days to return to training (which remained significant).

8.3 DISCUSSION AND CLINICAL RELEVANCE OF THE MAIN FINDINGS IN THIS THESIS

Incidence and risk factors associated with ARinf, including SARS-CoV-2 infection, in athletes

Time loss from ARinf, can have a major impact on an athlete's availability to train or compete, with subsequent consequences regarding performance or financial income. It is therefore important to determine the incidence of SARS-Cov-2 in different time intervals/training phases, and to explore risks associated with infection, to improve risk mitigation strategies and decrease the burden on health and sports performance.

The incidence of "All ARinf" of 0.31 per 1000 player days in our cohort, was lower than the 4.9 per 1000 player days reported in a systematic review on ARinf in athletes prior to the COVID-19 pandemic.[50] However, our findings were analysed per team (not individuals), and based on self-reported data that may have underreported incidence during competition due to timing of data collection. The global, national and institutional measures to prevent the spread of SARS-CoV-2 infection, is another important explanation for the lower incidence of ARinf in our study, but these measures are not always practical in the contact sport setting, e.g. physical distancing. The incidence of SARS-CoV-2 infection (0.23 per 1000 player days) was also lower than the 1.23 per 1000 player days reported in another study on SARS-CoV-2 infection in rugby players.[51] This study differed from our study as players were tested routinely and hence asymptomatic cases were reported. Similar to our findings, this study also reported a higher incidence during contact phases. Routine testing to identify asymptomatic athletes, prompt diagnosis of a pathogen and appropriate isolation of infected athletes, might prevent the spread of ARinf, including SARS-CoV-2, but this is not always feasible. In our study, no other factors associated with ARinf, including SARS-CoV-2

infection, were identified. To reduce the impact of ARinf in athletes, risk mitigation planning, adoption of personal hygiene countermeasures, identification of individual athlete risk factors, and sport specific countermeasures should be considered.

RTS guidelines after ARInf, including SARS-CoV-2 infection, in athletes by clinical criteria and laboratory investigations

After an acute ARinf resulting in time loss, the SEM should provide an athlete with guidelines to return to sport. Before training can commence, important clinical decisions are required to identify and mitigate against potential medical complications. To assist the SEM, an International Olympic Committee (IOC) expert group recently proposed a RTS algorithm in a consensus statement on ARinf in athletes.[8] The first step in this algorithm is to determine the severity of ARinf based on: 1) symptoms during the acute phase of infection, and 2) evidence of multi-organ involvement (clinical findings and laboratory investigations). Once an athlete returns to training, the athlete progressively increases training load until full performance is reached (RTFP). To our knowledge, the algorithm proposed by the IOC consensus group has not been verified. In the series of studies reported in this thesis, we report novel data that support aspects of the step in the IOC consensus algorithm.

From all the research studies reported in this thesis the key finding is the importance of obtaining a detailed history on the symptoms during the acute phase of a SARS-CoV-2 infection in athletes. Acute symptoms could be categorised in three anatomical regions: “nose and throat”, “chest and neck” and “whole body” (systemic) symptoms (Table 1). Our studies specifically show highly significant associations between the presence of certain acute symptoms, total number of acute symptoms, as well as the location of symptoms by anatomical region with the following key outcome variables: multi-organ involvement, days to RTT, and days to RTFP.

These novel findings, address three key objectives of the PhD thesis. We acknowledge that symptoms are self-reported and the findings of univariate analyses should not be over-interpreted. However, from the univariate analysis data on specific acute symptoms may still provide useful clinical information.

Table 1: The presence and number of symptoms by anatomical region and specific symptoms during the acute phase of the infection, associated with return to training and return to full performance (univariate and multiple model analyses)

Anatomical region	RETURN TO TRAINING				RETURN TO FULL PERFORMANCE			
	Univariate #		Multiple models		Univariate #		Multiple models	
	Presence	Number	Presence	Number	Presence	Number	Presence	Number
Nose and throat								
Any nose throat		✓		✓		✓	-	✓
Sore/scratchy throat							-	
Hoarseness	✓						-	
Blocked/plugged nose							-	
Runny nose							-	
Sinus pressure							-	
Sneezing							-	
Altered/loss sense smell							-	
Altered/loss sense taste							-	
Chest and neck								
Any chest and neck	✓	✓	✓	✓	✓	✓	-	✓
Dry cough							-	
Wet cough							-	
Difficulty in breathing	✓						-	
Fast breathing/ shortness of breath							-	
Chest pain/pressure	✓				✓		-	
Chest tightness					✓		-	
Headache					✓		-	
Red/watery/scratchy eyes							-	
Whole body/systemic								
ANY whole body/systemic	✓	✓		✓	✓	✓	-	✓
Fever					✓		-	
Chills	✓				✓		-	
Excessive fatigue	✓				✓		-	
General muscle aches and pains					✓		-	
Skin rash							-	
Abdominal pain	✓						-	
Nausea					✓		-	
Vomiting							-	
Diarrhoea							-	
Loss of appetite	✓				✓		-	
All symptoms	-	✓	-	✓	-	✓	-	✓

-Test not performed as not statistically indicated

Reporting on return to full performance was only done for the symptomatic group

Clinical relevance of main findings

Presence of symptoms during the acute phase of SARS-CoV-2 infection on RTS time points in athletes

- Clinically relevant findings related to the presence of symptoms during the acute phase of the infection are as follows: Any "chest or neck symptoms", and specifically chest pain, was associated with both prolonged RTT and RTFP. Lower respiratory symptoms have previously also been associated with a higher risk of time loss[40] and exertional chest pain warrants further investigations as it may indicated underlying cardiac pathology.[39]
- Difficulty in breathing was associated with prolonged RTT, whilst chest tightness was related to prolonged RTFP. Previous studies also found cough and shortness of breath as common persisting symptoms in both athletes[39] as well as the general population.[52]
- The presence of any "whole body" symptoms, specifically excessive fatigue and chills, was significantly associated with increased risk of prolonged RTT and RTFP. Excessive fatigue was associated with prolonged RTT[41] and is commonly reported as a persistent symptom in athletes.[53 54]
- Other symptoms e.g. headache and general muscle aches may not only prolong RTFP, but also challenge the exercising athlete's ability to perform.

Number of symptoms during the acute phase of SARS-CoV-2 infection on RTS time points in athletes

Clinically relevant findings related to the number of acute symptoms during the acute phase of the infection in anatomical regions are as follows:

- An increase in number of acute symptoms in each anatomical region is associated with both prolonged RTT and RTFP.
- An increase in the total number of acute symptoms, is also associated with both time points (RTT and RTFP). Thus, with the addition of one more acute symptom in each anatomical region, or in increase in the total number of acute symptoms, the risk of prolonged RTT and RTFP increases.
- The number of organs involved increase significantly if more than 5 acute symptoms are present during the acute phase of infection.
- Total number of acute symptoms may be an indicator of the severity of SARS-CoV-2 infection in athletes.

Multi-organ involvement in athletes with SARS-CoV-2 infection (residual symptoms, clinical signs, and laboratory investigations)

Clinically relevant findings related to multi-organ involvement in athletes with SARS-CoV-2 infection are as follows:

- Increased number of acute symptoms (>10) is associated with a higher frequency of residual symptoms, specifically respiratory (upper and lower) and neurological symptoms.
- Residual symptoms in most organ systems are not strongly associated with abnormal clinical signs or abnormal laboratory investigations except for the upper respiratory tract (clinical signs correlated with symptoms).
- The total number of acute symptoms was not associated with abnormal clinical findings or abnormal special investigations. However, participant numbers were too few for comparisons of all variables.
- The most reported residual symptoms, by organ system, were: 1) respiratory (lower: shortness of breath and dry cough and upper: blocked nose and sinus pressure), 2) neurological (excessive fatigue and headache), and 3) cardiovascular (racing heart). This finding is similar to that reported in previous studies where prolonged symptoms were fatigue, dry cough, headache and dyspnoea in both the athletic population[40] and general population.[55]
- The total number of acute phase symptoms may be the most important clinical indicator of the severity of SARS-CoV-2 infection in athletes

Additional factors associated with RTS time points and multi-organ involvement after SARS-CoV-2 infection in athletes

Clinically relevant findings related to additional factors associated with RTS time points and multi-organ involvement in athletes with SARS-CoV-2 infection are shown in Table 2.

Table 2: Factors associated with return to training and return to full performance (univariate analysis)

Factors	RTT (Univariate model)	RTFP (Univariate model)	Multi-organ involvement (Univariate model)
Demographics			
Female	✓	✓	✓
Age			
Sport participation			
Level of sport (professional)			
Type of sport (endurance)		✓	✓
History on co-morbidities			
Number of co-morbidities		✓	
Respiratory illness		✓	
Pre-infection training			
7 Days before infection	✓		
2-5 Weeks before infection			
Days to RTT		✓	

RTT, return to training; RTFP, return to full performance

A summary of clinically relevant findings related to additional factors associated with RTS time points and multi-organ involvement in athletes with SARS-CoV-2 infection are:

- Female athletes have a higher chance of prolonged RTT and RTFP. It was also previously documented that female athletes are at higher risk for prolonged SARS-CoV-2 symptoms.[40]
- Female athletes also have greater number of symptoms during the acute phase of infection compared to males. This finding is in contrast with a previous study reporting that female athletes were mostly asymptomatic (a cohort of 111 athletes).[44]
- Endurance athletes were also likely to return to performance over a longer period compared with other sport types.
- A history of co-morbidities, especially respiratory disease (predominately asthma), may be associated with prolonged RTFP. Although asthma was the most commonly reported co-morbidity, it may be underreported.[56 57]

8.4 TRANSLATION OF THE RESEARCH FINDINGS REPORTED IN THIS THESIS

The main findings of this research, contribute to the knowledge on the scientific basis for RTS guidelines as follows:

- Obtaining a detailed history of acute phase symptoms is an inexpensive tool that is of great importance to evaluate severity of acute SARS-CoV-2 infection and can guide subsequent steps for medical clearance before RTT.
- Special attention should be given to the presence of specific symptoms in the "chest and neck" and "whole body" regions.
- The total number of acute symptoms, as well as the number of acute symptoms in each anatomical region are important predictors of RTS time points and also indicate risk of multi-organ involvement (Figure 1).
- Athletes with asymptomatic and mild SARS-CoV-2 infection, do not require routine medical assessments.
- Athletes with moderate to severe SARS-CoV-2 infection are advised to seek medical care including a physical examination with individualised laboratory investigations, based on previous medical history, new/persisting symptoms of concern or poor exercise tolerance.
- All residual symptoms, clinical signs, and laboratory investigations, should be interpreted on an individual basis.
- RTT guidelines should take an individual's residual symptoms, clinical findings, previous medical history and risk factors into consideration.
- All athletes with SARS-CoV-2 infection should be monitored throughout the RTS process, until full performance is reached, as some may only develop new or worsening symptoms once exercise commences or progresses.

8.5 LIMITATIONS OF THIS THESIS

The limitations of the literature reviews and the original studies were discussed in depth in each individual chapter.

General limitations of the studies in the thesis are:

- The effect of both fear for a novel virus and the possible medical consequences for athletes could affect the general mental well-being of athletes with SARS-CoV-2. This, in turn, could affect RTT and RTFP time points, but these potential effects were not within the scope of this thesis.

- The study participants ranged from 18 to 60 years. RTS time points may differ significantly for individuals in different age categories. However, age was not associated with RTT or RTFP in this study.
- The number of participants were not adequate for all statistical analyses in the original research studies.

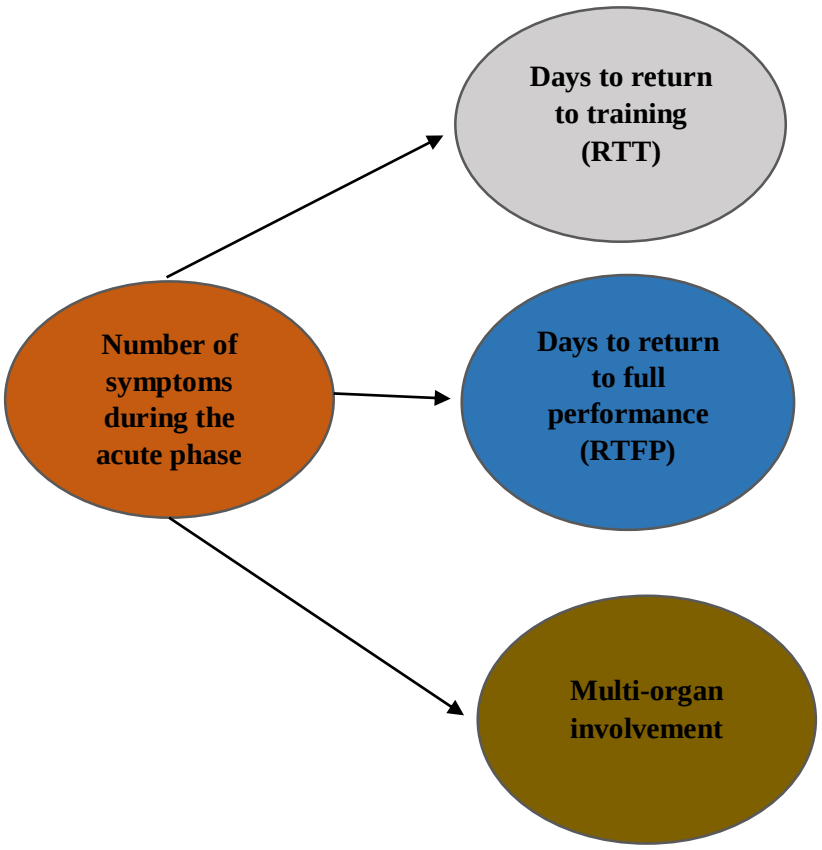

Figure 1: The association between number of symptoms during the acute phase of infection and return to training, return to full performance and multi-organ involvement

8.6 RECOMMENDATIONS FOR FUTURE RESEARCH

We recommend future studies to determine RTS parameters and time points in larger cohorts of vaccinated athletes, different SARS-CoV-2 variants, and ARinf in athletes that are caused by other pathogens to gain more insight into RTS guidelines. The effect of mental health on RTS outcomes after ARinf, including SARS-CoV-2, should be investigated. Studies should also be conducted on RTFP in different populations and the association between multi-organ

involvement and RTFP should be explored. Due to the high burden of ARinf on athlete health and the ability to train, these very common acute illnesses in athletes justify further investigations. We suggest that future research studies use standardised definitions and measuring units, in order for data to be compared. Global collaboration will assist in obtaining valuable data on all sporting communities.

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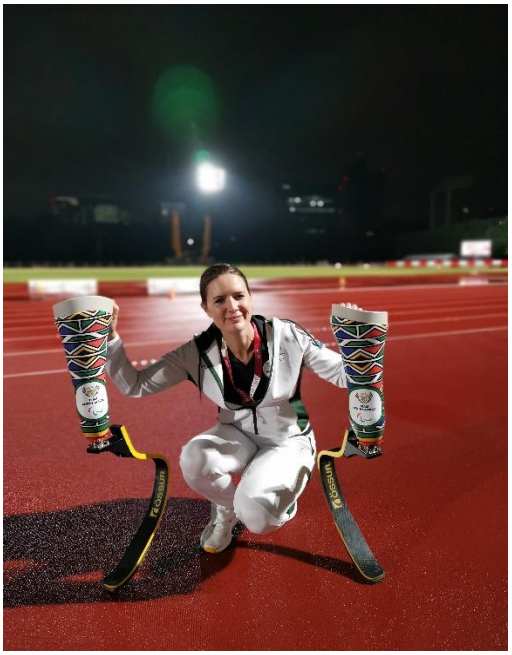
ABOUT THE AUTHOR



I (Carolette Snyders), am a sport physician and clinical researcher. My career in Sports Medicine started in 2009. Since then, I had the opportunity to be part of the medical team serving South African sports teams at 2 Commonwealth Games (2018 and 2022), and was privileged to accompany the South African Paralympians to Rio (2106) and Tokyo Paralympic Games (2021). The need for translational research for acute respiratory infections in the athlete, became a practical necessity during normal clinical practice, and especially during time of competition and travelling with athletes.

I therefore commenced on this PhD journey in 2019, in the quest to combine research with clinical medicine, thus wearing both clinical and researcher 'hats' as part of my daily practice in medicine.

I enjoy new opportunities and challenges, with a desire to always be a student, in medicine and in life.

GRATITUDE

I would not be me without my family, and therefore would like to express my sincere gratitude to:

Neil, you scarified so much to enable me to pursuit so many – completing this study, travel with sport teams or visiting conferences to feed my hunger to know more. Thank you, without you, this would not have been possible. Love and respect you!

Juan, our kind hearted and adventurous boy. You are wise, and you are kind. Your attention to detail and love for adventure, is true to who you are. Thank you for allowing me late nights of work and shortened days to play. I am looking forward to see the man you will become! Love you and proud you, always!

Xander, you are truly a ray of sunshine with a contagious laugh. You bring light and joy wherever you go. You have a way of enjoying life and people love your company. Stay the way you are – you have so much to contribute to this world! Love you Xan, forever!

Dadda and Mom, you taught me integrity, honesty, showing up and to keep on going, even if things get tough. You instilled so many values in me, by what you taught me, but more by how you both live. I honour and love you sincerely!

Jealine, thank you cheering me on! I appreciate your support, your encouragement and for just been my older Sis. You chose a road less travelled, and I admire you for that!

God, you showed me time and time again that you are indeed able to do *exceedingly, abundantly, above* what I can pray of think. Thank you -may I always remember this!

APPENDICES
ETHICAL APPROVAL

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH GCP guidelines and has US Federal wide Assurance.

- FWA 00002567. Approved dd 18 March 2022 and Expires 18 March 2027.
- IORG #: IORG0001702 OMB No. 0990-0278 Approval for use through August 31, 2023

Faculty of Health Sciences **Research Ethics Committee**

15 September 2022

Approval Certificate
Annual Renewal

Dear Dr C Snyders,

Ethics Reference No.: 751/2019 – Line 5
Title: Return to sport guidelines in athletes with selected acute respiratory infections, including COVID-19, based on clinical criteria and laboratory investigations.

The **Annual Renewal** as supported by documents received between 2022-08-22 and 2022-09-14 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2022-09-14 as resolved by its quorate meeting.

Please note the following about your ethics approval:

- Renewal of ethics approval is valid for 1 year, subsequent annual renewal will become due on 2023-09-15.
- Please remember to use your protocol number (751/2019) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers
MBChB, MMed (Int), MPharmMed, PhD
***Deputy Chairperson** of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2016 (Department of Health)

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Lefapha la Disciplene tsa Maphelo

CHAPTER 2: Supplementary material

Acute respiratory illness and return to sport: a systematic review and meta-analysis by a subgroup of the IOC consensus on 'acute respiratory illness in the athlete'

Review

Acute respiratory illness and return to sport: a systematic review and meta-analysis by a subgroup of the IOC consensus on 'acute respiratory illness in the athlete'

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjsports-2021-104719).

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ABSTRACT

Objective To determine the days until return to sport (RTS) after acute respiratory illness (ARill), frequency of time loss after ARill resulting in >1 day lost from training/competition, and symptom duration (days) of ARill in athletes.

Design Systematic review and meta-analysis.

Data sources PubMed, EBSCOhost, Web of Science, January 1990–July 2020.

Eligibility criteria Original research articles published in English on athletes/military recruits (15–65 years) with symptoms/diagnosis of an ARill and reporting any of the following: days until RTS after ARill, frequency (%) of time loss >1 day after ARill or symptom duration (days) of ARill.

Results 767 articles were identified; 54 were included (n=31 065 athletes). 4 studies reported days until RTS (range: 0–8.5 days). Frequency (%) of time loss >1 day after ARill was 20.4% (95% CI 15.3% to 25.4%). The mean symptom duration for all ARill was 7.1 days (95% CI 6.2 to 8.0). Results were similar between subgroups: pathological classification (acute respiratory infection (ARinf) vs undiagnosed ARill), anatomical classification (upper vs general ARill) or diagnostic method of ARinf (symptoms, physical examination, special investigations identifying pathogens).

Conclusions In 80% of ARill in athletes, no days were lost from training/competition. The mean duration of ARill symptoms in athletes was 7 days. Outcomes were not influenced by pathological or anatomical classification of ARill, or in ARinf diagnosed by various methods. Current data are limited, and future studies with standardised approaches to definitions, diagnostic methods and classifications of ARill are needed to obtain detailed clinical, laboratory and specific pathogen data to inform RTS.

PROSPERO registration number CRD42020160479.

INTRODUCTION

The International Olympic Committee is committed to protecting the health of the athlete.[1] Acute illness threatens athlete health and well-being, and can lead to interruption of training, withdrawal from competition and financial loss for professional athletes.[2 3] An acute illness causing delayed time to return to sport (RTS) (training and/or competition) is referred to as a 'time loss' illness.[4]

In athletes, the respiratory tract accounts for ~50% of all acute illness episodes,[5–9] and the majority of acute respiratory illnesses (ARill) in athletes are acute respiratory infections (ARinf).[6–10] The annual incidence of ARinf in the general adult population is about 2–3 episodes per year.[11] Physically active individuals typically have a lower incidence of ARinf compared with sedentary individuals, but competitive athletes may be more susceptible to ARinf, especially during periods of intense training and competition (J-shaped curve).[12] Elite athletes accustomed to very high training and competition loads may be less prone to ARinf (S-shaped curve).[13–15]

The sport and exercise medicine (SEM) physician is responsible for guiding the athlete with recent ARill to full and safe sports participation in the shortest possible time, while minimising the risk of potential medical complications. Evidence-based clinical guidelines to assist the SEM physician to decide on RTS after ARinf are lacking. RTS can be defined as 'the time (days after the onset of an injury or illness), when the ill or injured athlete can return to preillness/injury level of activity and full training and competitive sports activities, with no limitation in performance or additional risk of medical complications'.[16 17]

Symptoms of an acute illness are widely used in RTS decision making, specifically for ARinf.[18–20] Historically, athletes with localised symptoms of ARinf above the neck (eg, sore throat, rhinorrhoea or nasal congestion) were advised that exercise can resume at a low intensity for a short duration, and if exercise is well tolerated, training can continue. If symptoms are below the neck (eg, fever, myalgia or cough), the athlete was advised to rest until symptoms have resolved. These guidelines are referred to as the 'neck check'.[19] There is no scientific evidence for these guidelines and the validity of the 'neck check' as a guide for RTS has been challenged.[21] Despite the lack of data, the presence and nature (type) of regional/systemic symptoms is still a key component of most clinical decision-making guidelines for RTS following ARinf in athletes.[22–24]

Several studies report the frequency (%) of ARill that result in interruption from training/competition for >1 day (% of time loss ARill), while other studies report the duration of symptoms (days) of ARill. The frequency (%) of time loss ARill is defined as the number of ARill that resulted in time

Online supplementary file 1: Specific search strategies

PubMed: (Rhinovirus OR Parainfluenza OR Adenovirus OR coronavirus OR "human metapneumovirus" OR enterovirus OR "respiratory syncytial virus" OR "bordetella pertussis" OR "chlamydophila pneumoniae" OR "mycoplasma pneumoniae" OR Rhinitis OR influenza OR "common cold" OR flu OR sinusitis OR "rhino sinusitis" OR "acute pharyngitis" OR tonsillitis OR pharyngitis OR epiglottitis OR laryngitis OR "Haemophilus influenzae" OR "Streptococcus pneumoniae" OR "Klebsiella pneumoniae" OR "Moraxella catarrhalis" OR pneumonia OR pneumoniae OR bronchitis OR "lung disease" OR "Respiratory tract disease*" OR "Respiratory illness*" OR "Respiratory tract infection*" OR "respiration disorder*" OR "respiratory system disease*" OR "upper respiratory tract illness*" OR "upper respiratory tract disease*" OR "Lower respiratory tract illness*" OR "Lower respiratory tract disease*" OR "Viral disease*" OR "pulmonary tuberculosis" OR "laryngopharyngeal reflux" OR "supraesophageal gastric reflux" OR "non-infective acute respiratory illness" OR "air pollution" OR chemical* OR "non-infective acute respiratory disease*" OR "non-infective acute respiratory tract illness" OR "non-infective acute respiratory tract disease" OR "air pollution" OR weather OR climate OR chlorin* OR allerg* OR (inhal* AND gas*) OR "air quality" OR rhinoconjunctivitis) AND (athlete* OR sport* OR exercise* OR "athletic population" OR "active population" OR "active individual" OR military) AND ("Normalisation of organ function*" OR "Return to sport" OR "return to play" OR "return to performance" OR "return to activity" OR "Return to Sport* Activities" OR "Resumption of Sport*Activity*" OR "sport* activity resumption" OR Recovery OR "Recovery of function" OR Convalescence OR "athlete availability" OR "return to training" OR clearance) NOT (COPD OR "chronic obstructive pulmonary disease" OR cancer OR animal* OR HIV OR "human immunodeficiency virus" OR AIDS OR "acquired immunodeficiency syndrome" OR post-operative OR postoperative OR preoperative OR pre-operative OR pre-surgery OR post-surgery OR food OR radiation OR "position statement" OR "consensus statement" OR "systematic review" OR infant OR "influenza pandemic" OR "water immersion" OR concussion OR psychology* OR diabetes OR "cystic fibrosis" OR congenital OR combat OR wound OR groin OR lupus OR cryotherapy OR sleep OR bronchiectasis OR elderly OR Hajj OR "cooling kit" OR alcohol OR hyperoxia OR EMG OR war) **Filters:** Humans, English, MEDLINE, from 1990 – 2020

EbscoHost: "Human AND (Rhinovirus OR Parainfluenza OR Adenovirus OR coronavirus OR “human metapneumovirus” OR enterovirus OR “respiratory syncytial virus” OR “bordetella pertussis” OR “chlamydophila pneumoniae” OR “mycoplasma pneumoniae” OR Rhinitis OR influenza OR “common cold” OR flu OR sinusitis OR “rhino sinusitis” OR “acute pharyngitis” OR tonsillitis OR pharyngitis OR epiglottitis OR laryngitis OR “Haemophilus influenzae” OR “Streptococcus pneumoniae” OR “Klebsiella pneumoniae” OR “Moraxella catarrhalis” OR pneumonia OR pneumoniae OR bronchitis OR “lung disease” OR “Respiratory tract disease*” OR “Respiratory illness*” OR “Respiratory tract infection*” OR “respiration disorder*” OR “respiratory system disease*” OR “upper respiratory tract illness*” OR “upper respiratory tract disease*” OR “Lower respiratory tract illness*” OR “Lower respiratory tract disease*” OR “Viral disease*” OR “pulmonary tuberculosis” OR “laryngopharyngeal reflux” OR “supraesophageal gastric reflux” OR “non-infective acute respiratory illness” OR “air pollution” OR chemical* OR “non-infective acute respiratory disease*” OR “non-infective acute respiratory tract illness” OR “non-infective acute respiratory tract disease” OR “air pollution” OR weather OR climate OR chlorin* OR allerg* OR (inhal* AND gas*) OR “air quality” OR rhinoconjunctivitis) AND (athlete* OR sport* OR exercise* OR “athletic population” OR “active population” OR “active individual” OR military) AND (“Normalisation of organ function*” OR “Return to sport” OR “return to play” OR “return to performance” OR “return to activity” OR “Return to Sport* Activities” OR “Resumption of Sport*Activity*” OR “sport* activity resumption” OR Recovery OR “Recovery of function” OR Convalescence OR “athlete availability” OR “return to training” OR clearance) NOT (COPD OR “chronic obstructive pulmonary disease” OR cancer OR animal* OR HIV OR “human immunodeficiency virus” OR AIDS OR “acquired immunodeficiency syndrome” OR post-operative OR postoperative OR preoperative OR pre-operative OR pre-surgery OR post-surgery OR food OR radiation OR “position statement” OR “consensus statement” OR “systematic review” OR infant OR “influenza pandemic” OR “water immersion” OR concussion OR psychology* OR diabetes OR “cystic fibrosis” OR congenital OR combat OR wound OR groin OR lupus OR cryotherapy OR sleep OR bronchiectasis OR elderly OR Hajj OR “cooling kit” OR alcohol OR hyperoxia OR EMG OR war) Published Date: 19910101-20200731; Document Type: Article

***Web of Science*:** TOPIC: (Human AND (Rhinovirus OR Parainfluenza OR Adenovirus OR coronavirus OR “human metapneumovirus” OR enterovirus OR “respiratory syncytial virus” OR “bordetella pertussis” OR “chlamydophila pneumoniae” OR “mycoplasma pneumoniae”

OR Rhinitis OR influenza OR “common cold” OR flu OR sinusitis OR “rhino sinusitis” OR “acute pharyngitis” OR tonsillitis OR pharyngitis OR epiglottitis OR laryngitis OR “Haemophilus influenzae” OR “Streptococcus pneumoniae” OR “Klebsiella pneumoniae” OR “Moraxella catarrhalis” OR pneumonia OR pneumoniae OR bronchitis OR “lung disease” OR “Respiratory tract disease*” OR “Respiratory illness*” OR “Respiratory tract infection*” OR “respiration disorder*” OR “respiratory system disease*” OR “upper respiratory tract illness*” OR “upper respiratory tract disease*” OR “Lower respiratory tract illness*” OR “Lower respiratory tract disease*” OR “Viral disease*” OR “pulmonary tuberculosis” OR “laryngopharyngeal reflux” OR “supraesophageal gastric reflux” OR “non-infective acute respiratory illness” OR “air pollution” OR chemical* OR “non-infective acute respiratory disease*” OR “non-infective acute respiratory tract illness” OR “non-infective acute respiratory tract disease” OR “air pollution” OR weather OR climate OR chlorin* OR allerg* OR (inhal* AND gas*) OR “air quality” OR rhinoconjunctivitis) AND (athlete* OR sport* OR exercise* OR “athletic population” OR “active population” OR “active individual” OR military) AND (“Normalisation of organ function*” OR “Return to sport” OR “return to play” OR “return to performance” OR “return to activity” OR “Return to Sport* Activities” OR “Resumption of Sport*Activity*” OR “sport* activity resumption” OR Recovery OR “Recovery of function” OR Convalescence OR “athlete availability” OR “return to training” OR clearance) NOT (COPD OR “chronic obstructive pulmonary disease” OR cancer OR animal* OR HIV OR “human immunodeficiency virus” OR AIDS OR “acquired immunodeficiency syndrome” OR post-operative OR postoperative OR preoperative OR pre-operative OR pre-surgery OR post-surgery OR food OR radiation OR “position statement” OR “consensus statement” OR “systematic review” OR infant OR “influenza pandemic” OR “water immersion” OR concussion OR psychology* OR diabetes OR “cystic fibrosis” OR congenital OR combat OR wound OR groin OR lupus OR cryotherapy OR sleep OR bronchiectasis OR elderly OR Hajj OR “cooling kit” OR alcohol OR hyperoxia OR EMG OR war))

Refined by: DOCUMENT TYPES: (ARTICLE) AND LANGUAGES: (ENGLISH)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=1990-2020

Online supplementary file 2: Modified Downs and Black Quality Assessment Checklist

Article Title and Date:		
Authors:		
	Description	**Answer (circle)**
REPORTING		
1	Is the hypothesis/aim/objective of the study clearly described?	Yes = 1 No = 0
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes = 1 No = 0
3	Are the characteristics of the patients included in the study clearly described?	Yes = 1 No = 0
4	Are the interventions of interest clearly described?	Yes = 1 No = 0
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes = 1 No = 0
6	Are the main findings of the study clearly described?	Yes = 1 No = 0
7	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes = 1 No = 0
8	Have all important adverse events that may be a consequence of the intervention been reported?	Yes = 1 No = 0
9	Have the characteristics of patients lost to follow-up been described?	Yes = 1 No = 0
10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes = 1 No = 0
EXTERNAL VALIDITY		
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes = 1 No = 0 Unable to determine = 0
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes = 1 No = 0 Unable to determine = 0
13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes = 1 No = 0 Unable to determine = 0
INTERNAL VALIDITY – BIAS		
14	Was an attempt made to blind study subjects to the intervention they have received?	Yes = 1 No = 0 Unable to determine = 0
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes = 1 No = 0 Unable to determine = 0
16	If any of the results of the study were based on “data dredging”, was this made clear?	Yes = 1 No = 0 Unable to determine = 0

17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes = 1 No = 0 Unable to determine = 0
18	Were the statistical tests used to assess the main outcomes appropriate?	Yes = 1 No = 0 Unable to determine = 0
19	Was compliance with the intervention/s reliable?	Yes = 1 No = 0 Unable to determine = 0
20	Were the main outcome measures used accurate (valid and reliable)?	Yes = 1 No = 0 Unable to determine = 0
INTERNAL VALIDITY – CONFOUNDING (SELECTION BIAS)		
21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes = 1 No = 0 Unable to determine = 0
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes = 1 No = 0 Unable to determine = 0
23	Were study subjects randomised to intervention groups?	Yes = 1 No = 0 Unable to determine = 0
24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes = 1 No = 0 Unable to determine = 0
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes = 1 No = 0 Unable to determine = 0
26	Were losses of patients to follow-up taken into account?	Yes = 1 No = 0 Unable to determine = 0
POWER		
27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Size of smallest intervention group Yes = 1 No = 0 Unable to determine = 0
Assessing the quality: excellent (11-13), good (9-10), fair (7-8), and poor (≤6)[1 2]		

This checklist has been adjusted to remove the questions pertaining to RCTs, as the review used only PO (participants and outcomes).

REFERENCES

1. Chudyk AM, Jutai JW, Petrella RJ, et al. Systematic review of hip fracture rehabilitation practices in the elderly. *Arch Phys Med Rehabil* 2009;90(2):246-62.
2. O'Connor SR, Tully MA, Ryan B, et al. Failure of a numerical quality assessment scale to identify potential risk of bias in a systematic review: a comparison study. *BMC Res Notes* 2015;8(1):224.

Online supplementary file 3: Publication statistics - Egger's test and Funnel plots

Publication statistics- Egger's test and Funnel plots

Figure 1:

Eggers test = intercept =0.45, t=0.40, p=0.699

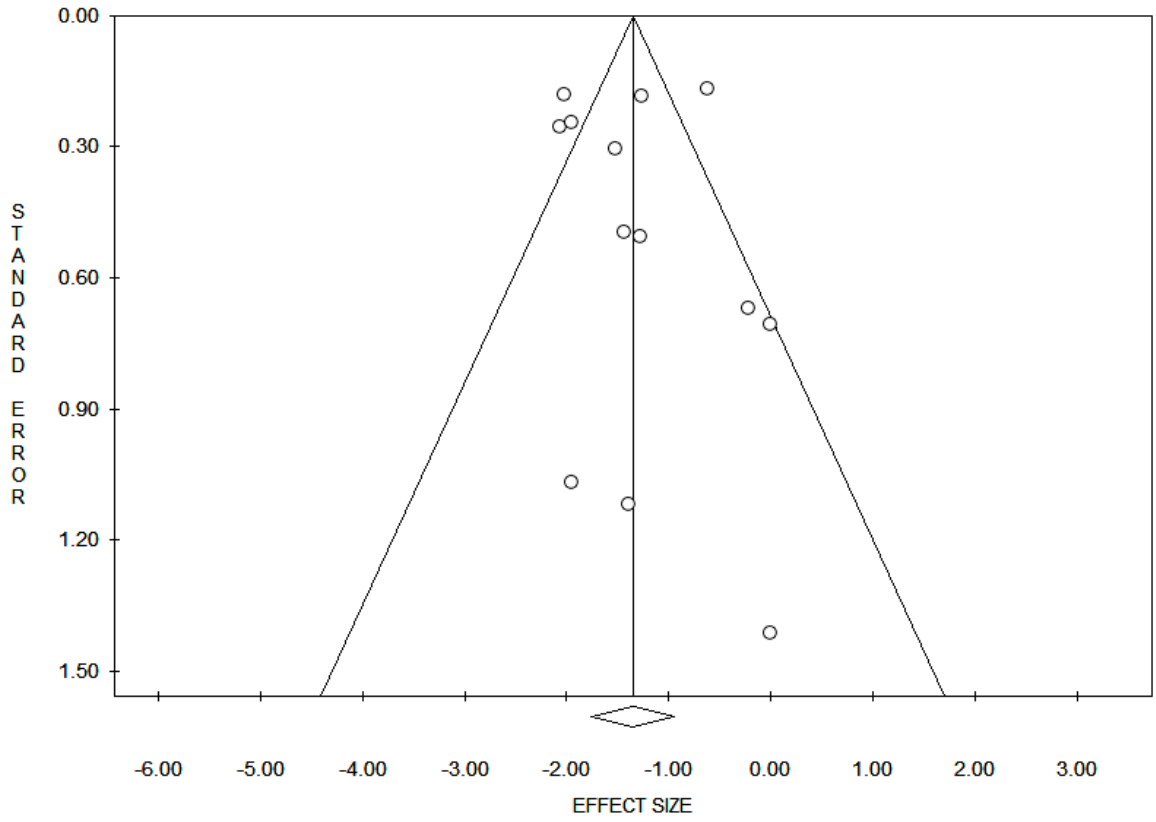


Figure 2:

Eggers test = intercept =0.47, t=0.26, p=0.802

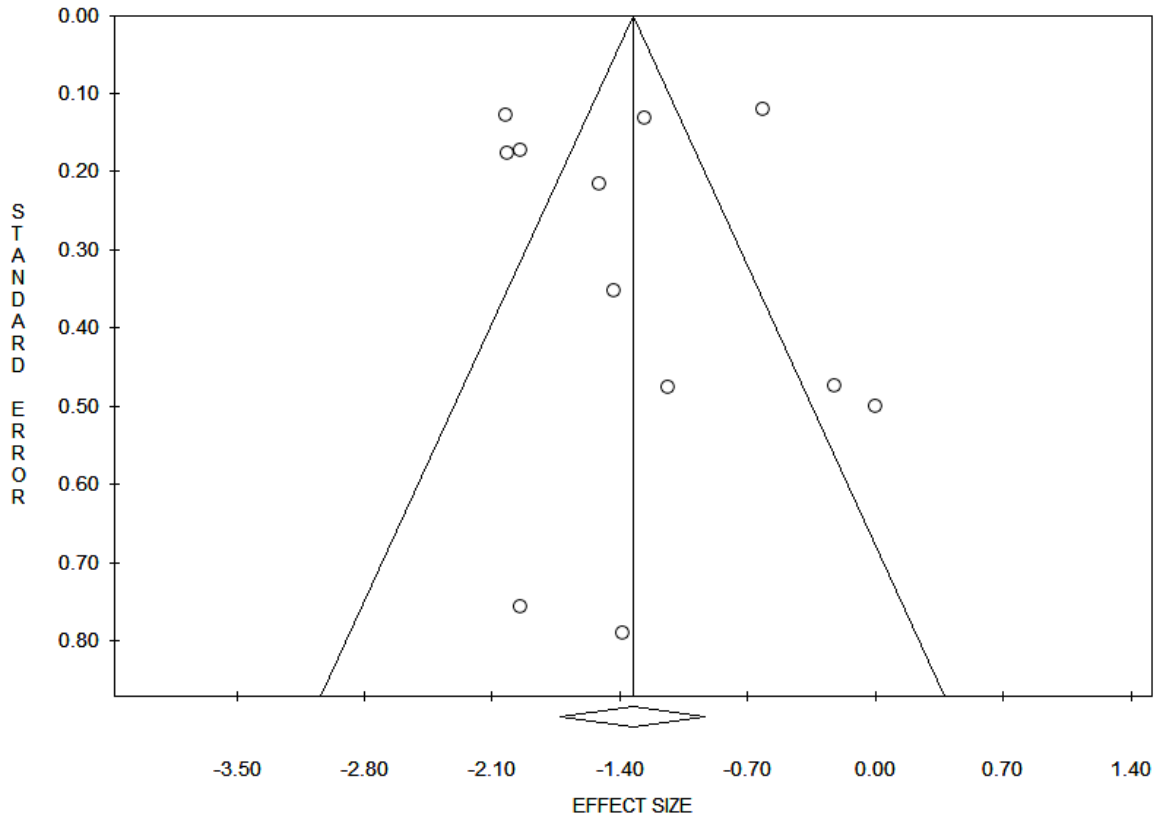


Figure 3:

Eggers test = intercept =0.30, t=0.21, p=0.839

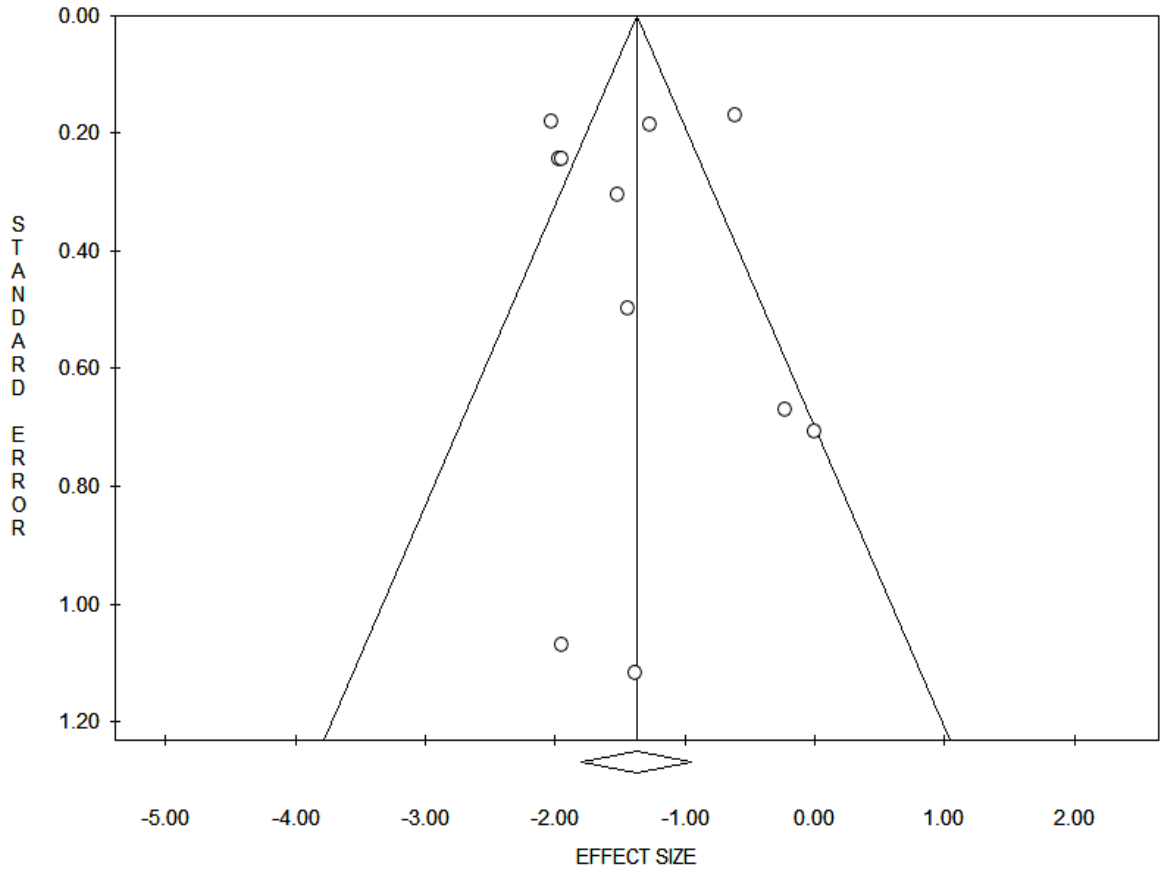


Figure 4:

Eggers test = intercept =4.63, t=2.26, p=0.031

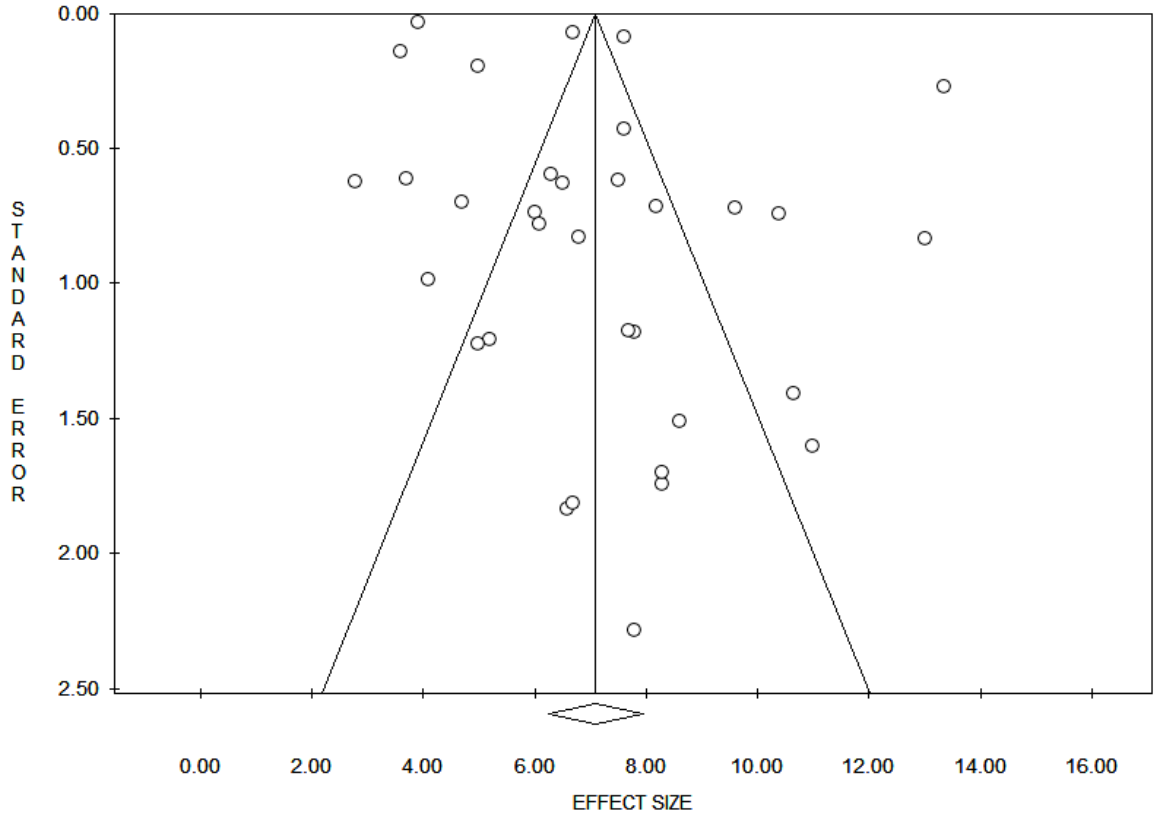
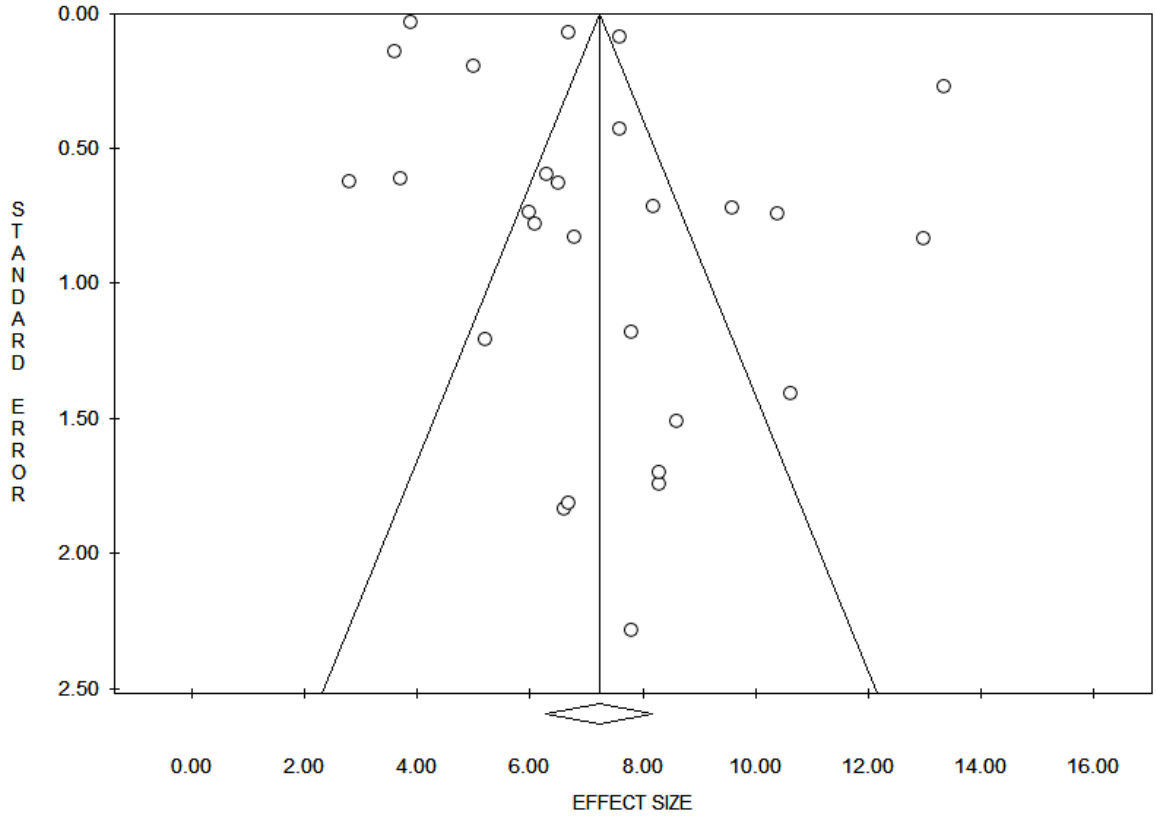


Figure 5:

Eggers test = intercept =5.36, t=2.12, p=0.044



Supplementary table A: Summary of articles: data extraction of the demographics

Author(s), Year	Participants (n, sex)	Age of participants (years) (mean ± SD)*	Study design *	Sport / Sporting Event	Level of participation	Length of surveillance (days)
Alonso et al (2012)	n=512 (sex not recorded)	26.9 ± 4.7	Prospective	2011 IAAF World Championships	Recreational / amateur / military	9
Bjørneboe et al (2016)	n=5070 player-seasons (all male)	Not recorded	Prospective cohort	Football	Elite / professional / international / national	1 460 (1 261 367 player-days)
Chesson et al (2020)	n=17 (all male)	17.7 ± 0.7	Observational prospective cohort	Rugby (league players)	Recreational / amateur / military	175
Cox et al (2010)	n=20 (M=16, F=4)	35.2 ± 8.4	RCT	Half-marathon 21.1 km	Recreational / amateur / military	35
Cox et al (2010)[a]	n=20 (all male)	27.3 ± 6.4	RCT	Running	Recreational / amateur / military	98
Cox et al (2008)[¥]	n=70 (M=51; F=19)	19.3 ± 2.6	Prospective study	Mixed	Elite / professional / international / national	420
Cox et al (2004)	n=20 (all males)	24.6 ± 3.0	RCT	Distance Runners	Elite / professional / international / national	120
Cunniffe et al (2011)	n=31 (all male)	26.5	Prospective	Rugby	Elite / professional / international / national	336
Da Boit et al (2015)	n=17 (M=9, F=6)	28.3 ± 6.4	RCT	General	Recreational / amateur / military	112
Davison et al (2020)	n=61 (sex unknown)	39.3 ± 11.5	RCT	Endurance athletes	Recreational / amateur / military	90
Derman et al (2019)	n=567 (M=433, F=134)	32.1 ± 10.3	Prospective	Winter Paralympics	Elite / professional / international / national	12

Derman et al (2014)	n=3329 (sex not recorded)	Not recorded	Prospective	Paralympics	Elite / professional / international / national	14
Dressendorfer et al (2002)	n=9 (all males)	24.7 ± 2.1	Prospective	Mountain bike cyclists	Recreational / amateur / military	98
Edouard et al (2015)	n=528 (sex not recorded)	25.3 ± 4.2	Prospective	2013 European Athletics Indoors	Elite / professional / international / national	4
Edouard et al (2014)	n=1244 (sex not recorded)	Not recorded	Prospective	2012 European Athletics championships	Elite / professional / international / national	5
Edouard et al (2013)	n=440 (sex not recorded)	25.2 ± 4.0	Prospective	2011 European Athletics Indoors	Elite / professional / international / national	3
Fahlman and Engels (2005)	n=75 (all male)	20.5 ± 1.5	Prospective with athlete and control groups	American Football	Recreational / amateur / military	365
Fricker et al (2005)	n=20 (all males)	24.2 ± 3.1	Prospective	Middle-distance runners	Elite / professional / international / national	120
Furusawa et al (2007)	Racers n=21 (all male)	42.0 ± 1.74 (Mean ± SE)	Prospective cohort	Wheelchair marathon racers	Recreational / amateur	44
Gleeson et al (2012)[a]	n=80 (M=46, F=34)	22.5 ± 4.0	Prospective	Endurance-based physical activity	Recreational / amateur / military	120
Gleeson et al (2011)	n=26	25 ± 9	RCT	Endurance athletes	Recreational / amateur / military	120
Hall et al (2007)	n=14 (sex not recorded)	24.9 ± 5.8	RCT	Active adults	Recreational / amateur / military	28
Hanstad et al (2011)	n=99 (M=74, F=25)	Not recorded	Prospective	2010 Winter Olympics - Norwegian team	Elite / professional / international / national	19
Haywood et al (2014)	n=38 (all male)	24.7 ± 3.6	RCT	Rugby	Elite / professional / international / national	28

He et al (2014)	n=210 (M=147, F=63)	20.4 ± 1.9 (male) 20.5 ± 3.1 (female)	Prospective cohort	Endurance	Recreational / amateur / military	112
He et al (2013)[a]	n=31 (sex not recorded)	21 ± 2	Prospective cohort	Endurance	Recreational / amateur / military	112
He et al (2013)[b]	n=225 (sex not recorded)	21 ± 3	Prospective cohort	Endurance	Recreational / amateur / military	112
Henson et al (2008)	n=21 (M=18, F=3)	46.0 ± 2.3	RCT	Ultra marathon runner	Recreational / amateur / military	14
Ihalainen et al (2015)	n=25 (all male)	34.6 ± 1.3	Prospective cohort	Endurance	Recreational / amateur / military	84
Kekkonen et al (2007)	n=71 (M=63, F=8)	40 Range (23-69)	RCT	Marathon	Recreational / amateur / military	146
Laaksi et al (2007)	n=756 (all male) Control subjects (normal Vit D) n=628 (time loss recorded in this group)	Not recorded	Prospective cohort	Military	Recreational / amateur / military	184
McFarlin et al (2013)	n=35 (M=20, F=15)	35 ± 11	RCT	Marathon runners	Recreational / amateur / military	28
Michalickova et al (2016)	n=19 (M=14, F=5)	22.8 ± 2.5	RCT	Mixed	Elite / professional / international / national	98
Nehlsen-Cannarella et al (2000)	n=20 (all female)	22.6 + 0.5 (Mean ± SEM)	Prospective cohort	Rowers	Elite / professional / international / national	60
Nieman et al 2008	n=17 (all male)	25.0 ± 2.2 (Mean ± SE)	RCT	Cyclists	Recreational / amateur / military	35
Nordstrøm et al (2020)	n=225 (all male)	Mean 24 Range (17-41)	Prospective cohort study	Ice hockey	Elite / professional / international / national	210

Orhant et al (2010)[¥]	n=81 (all male)	Range (17–34)	Prospective cohort	Soccer	Elite / professional / international / national	1095
Orysiak et al (2017)	n=27 (all male)	16.5 ± 0.5	Prospective cohort	Ice hockey	Recreational / amateur / military	168
Pacque et al (2007)	n=17 (M=13, F=4)	41.5 ± 8.2	Prospective cohort	Ultra endurance running	Recreational / amateur / military	28
Peters et al (2004)	n=19 (all males); fast well trained runners (n=9), slow less trained runners (n=10)	35.4 ± 1.84 (fast well trained runners) 41.4 ± 2.77 (slow well trained runners) (Mean ± SEM)	Prospective cohort	Marathon runners	Recreational / amateur / military	14
Pyne et al (2001)	n=41 (M=21, F=20)	Range (15-27)	Prospective	Swimming	Elite / professional / international / national	42
Rama et al (2013)	n=19 (M=13, F=6)	17.2 ± 1.3 (male) 15.8 ± 0.8 (female)	Prospective cohort	Swimming	Elite / professional / international / national	203
Sawczuk et al (2020)	n=22 (M=16; F=6)	16.8 ± 0.5	Prospective longitudinal study	Mixed	Recreational / amateur / military	266
Schwellnus et al (2012)[¥]	n=259 (all male)	Not recorded	Prospective cohort	Rugby	Elite / professional / international / national	112
Soligard et al (2017)	n=11274 (M=6185, F= 5089)	Not recorded	Prospective cohort	Summer Olympics	Elite / professional / international / national	17
Somerville et al (2019)	n=12 (M=4, F=8)	16.5 ± 0.5	RCT	Hockey, football, netball	Recreational / amateur / military	63

Somerville et al (2019)[a]	Cohort 2 (school rugby) n=15; cohort 3 (school rugby) n=24, amateur n=18, total n=57 (all male)	Not recorded	Longitudinal cohort	Rugby	Recreational / amateur / military	273
Somerville et al (2019)[b]	Professional n=24 (all male)	Not recorded	Longitudinal cohort	Rugby	Elite / professional / international / national	273
Spence et al (2007)[¥]	n=63 (M=35, F=28)	22.5 ± 3.8 (elite) 25.2 ± 3.6 (recreational)	Prospective	Triathlon Cycling	Elite / professional / international / national	150
Steffen et al (2019)	n=3 984 (M=2002, F=1982)	Range (15-18)	Prospective cohort	Youth Summer Olympics	Elite / professional / international / national	13
Stephenson et al (2019)	n=7 (M=6 male, F=1)	30 ± 10	Prospective cohort	Para triathletes (mixed impairment)	Elite / professional / international / national	238
Svendsen et al (2016)	n=37 (M=22, F=17)	>18	Retrospective cohort	Cross country ski	Elite / professional / international / national	2889
Tiollier et al (2005)[¥]	n=21 (all male)	21 ± 2	Prospective cohort	Military	Recreational / amateur / military	33
Valtonen et al (2019)[¥]	n=44 (M=31, F=13)	27 ± 6	Prospective observational study	Winter Olympics	Elite / professional / international / national	21
West et al (2011)	n=50 (M=33; F=17)	36.4 ± 8.9 (male) 35.6 ± 10.2 (female)	RCT	Cyclists and triathletes	Recreational / amateur / military	105

Online supplementary table B: Summary of articles - data extraction by classification and outcomes

Author(s), Year	Classification			Outcomes						
	Method of diagnosis	**Pathological classification**	**Anatomical classification**	**Total number ARill/ARinf, number of ARill episodes or number of participants with ARill/ARinf**	**Time Loss ARill (>1 day) (n; %)**	**Days lost per ARill (days and mean ± SD)***	**Days lost (total days lost/ illness and total illnesses)**	**Symptom duration in days (mean ± SD or average) ***	**Duration of symptoms (days and number of athletes)**	**Other outcomes**
Alonso et al (2012)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARill/ARinf	Total upper ARill n=49 Upper ARinf n=23	n=5 (5/23) 21% of upper ARinf					
Bjørneboe et al (2016)	Physician (diagnosis by history and clinical examination)	Undiagnosed ARill	General (upper/lower) ARill	ARill episodes n=1110						Illness burden 3.2 absence days/1000 player-days
Chesson et al (2020)	Self-reported symptoms only	Undiagnosed ARill	General (upper/lower) ARill	ARill n=15		Time loss (days) due to ARill n=12 days				Total days lost due to all illness n=19. Total days lost to ARill n=12 (63.2% of all time loss illnesses)

Cox et al (2010)	Self-reported symptoms with checklist and algorithm to diagnose infections	Undiagnosed ARill	Upper ARill	Upper ARill n=14				4.1 ± 3.7		
Cox et al (2010)[a]	Self-reported symptoms with physician check (no examination)	Suspected ARinf	General (upper/lower) ARinf	ARinf episodes n=9				Mean 8 (Range not specified)	Total days all ARinf n=72	
Cox et al (2008)[a]	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARill/ARinf	All upper ARill episodes n=70 (confirmed upper ARinf pathogen identified n=21/70 (30%)				6.8 ± 3.8		50% of the athletes modified, 31% ceased all training, and 19% reduced their training volume or intensity
Cox et al (2008)[b]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Suspected upper ARinf (PCR negative but abnormal blood results) n=19/70 (27%)				6.1 ± 3.4		

Cox et al (2008)[c]	Physician (diagnosis by history and clinical examination)	Undiagnosed ARill	Upper ARill	Undiagnosed ARill n=30/70 (43%)				7.5 ± 3.4		
Cox et al (2004)	Self-reported symptoms with physician check (no examination)	Suspected ARinf	Upper ARinf	Upper ARinf n=6 in placebo month				Mean 5 Range (2-14)		
Cunniffe et al (2011)	Self-reported symptoms with physician check (no examination)	Undiagnosed ARill	Upper ARill	Upper ARill n=123				Mean 4.7 Range (2-33)		In all ARill, 14% reported reduced activity, 8.6% felt need to go to bed
Da Boit et al (2015)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf n=8				2.79 ± 1.76		
Davison et al (2020)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Total upper ARinf n=130 episodes		Days lost 3.5 ± 5.0		10.4 ± 8.5		Reduced training 3.4 ± 5.1 (Mean ± SD)

Derman et al (2019)	Physician (diagnosis by history and clinical examination)	Undiagnosed ARill	General (upper/lower) ARill	All ARill n=28		Days lost n=9				
Derman et al (2014)	Physician (diagnosis by history and clinical examination)	Undiagnosed ARill	General (upper/lower) ARillf	All ARill n=152	n=19 (19/152) 12.5% of all ARill					
Dressendorfer et al (2002)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf n=4 (including 1 case influenza)	n=1 (influenza case) (1/5) 20% of upper ARinf	Influenza time loss days n=7 days; other upper ARinf time loss days n=0				
Edouard et al (2015)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf n=8	n=4 (4/8) 50% of all upper ARinf					
Edouard et al (2014)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf n=9	n=4 (4/9) 44% of upper ARinf					Upper ARinf time loss n=4, all time-loss illness n=6 (66.7% of all time loss illnesses)

Edouard et al (2013)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf n=8	n=1 (1/8) 12.5% of upper ARinf					
Fahlman and Engels (2005)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf n=174				13.3 ± 3.6		
Fricker et al (2005)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	15 athletes reported at least one episode of upper ARinf with mean number of episodes 2.5 (range 1-5)				Mean 8.3 Range (2-44)		
Furusawa et al (2007)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Number of racers with ARinf symptoms n=8 ("throughout experiment") n=4 (post-race)						

Gleeson et al (2012)[a]	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	At least one week with upper ARinf n=50, ≥3 weeks with upper ARinf n=24				3.6 ± 1.0		
Gleeson et al (2011)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Number of ARinf episodes 2.1 ± 1.2 (Mean ± SD)				7.6 ± 3.2		
Hall et al (2007)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf n=7				8.6 ± 1.5 (Mean ± SE)		
Hanstad et al (2011)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Total ARinf n=4; Infectious mononucleosis n=1, Upper ARinf n=3						n=1 did not compete, n=2 missed one competition, n=1 missed a relay for example
Haywood et al (2014)	Self-reported symptoms with checklist and algorithm	Suspected ARinf	Upper ARinf	Players with upper ARinf symptoms n=19				6.7 ± 7.9		

	to diagnose infections									
He et al (2014)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf symptoms n=92				11.6 ± 6.8 (males) 15.5 ± 9.3 (females) Mean 13 (all)		
He et al (2013)[a]	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Number of ARinf episodes 1.0 ± 1.1 (Mean ± SD)				8.2 ± 4.0		
He et al (2013)[b]	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Participant with ≥ 1 episode of upper ARinf n=103				Mean 5 Range (5-7) (optimal Vit D n=3) Mean 8 Range (6-9) (adequate Vit D n=56) Mean 8 Range (5-14) (inadequate Vit D n=27) Mean 13 Range (10-17) (deficient Vit D n=12)		Training negatively affected in 70% of athletes with upper ARinf and training load reduced by an average of 24%.

Henson et al (2008)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf n=5					Total sick days n=29 (for 5 ill athletes)	
Ihalainen et al (2015)	Self-reported symptoms only	Undiagnosed ARill	Upper ARill	Episodes of upper ARill symptoms n=19				11 ± 7		
Kekkonen et al (2007)	Self-reported symptoms only	Suspected ARinf	UpperARinf	Upper ARinf n=28				6.3 ± 4.3 (training group) 4.2 ± 2.2 (post-marathon group)		
Laaksi et al (2007)	Physician (diagnosis by history and clinical examination)	Suspected ARinf	General (upper/lower) ARinf			Median: 2; Q1-Q3: 0–4				
McFarlin et al (2013)	Self-reported symptoms only	Suspected ARinf	Upper ARinf					3.9 ± 0.2		
Michalickova et al (2016)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Athletes with upper ARinf n=11		Total days without training n=1.7 ± 2.3		10.6 ± 4.7	Infected days n=132 in 11 athletes	Proportion of athletes reporting impaired training 42%

Nehlsen-Cannarella et al (2000)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf					5.2 ± 1.2 (Mean ± SE)		
Nieman et al 2008	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf n=6				3.7 ± 0.6 (Mean ± SE)		
Nordstrøm et al (2020)	Self-reported symptoms only	Undiagnosed ARill	General (upper/lower) ARill	All ARill n=151	n=53 (53/151) 35.1% of ARill		ARill total days lost n=280, total number of ARill n=151			Total days lost due to ARill n=280 (59.8% of all time loss illnesses)
Orhant et al (2010)[a]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf n=151	n=17 (17/151) 11.3% of all upper ARinf	Days lost n=34	Days lost per episode 2.0	Mean 3.1 (Range not specified)		
Orhant et al (2010)[b]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Lower ARinf	Lower ARinf n=4	n=2 (2/4) 50% of all lower ARinf	Days lost n=5	Days lost per episode 2.5	Mean 4.8 (Range not specified)		

Orysiak et al (2017)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf n=59				6.3 ± 4.6	Total symptom days n=427 in 27 athletes	
Pacque et al (2007)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf: Pre-race n=4, post-race n=3				Average 8.5 (pre-race period) Average 6 (post-race period)	Total symptom days n=34 (pre-race) n=18 (post-race)	
Peters et al (2004)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf Fast well trained (FWT) n=5 Slow less trained (SLT) n=4				Average 4.3 (FWT) Average 3.5 (SLT)		
Pyne et al (2001)	Physician (diagnosis by history and clinical examination)	Undiagnosed ARill	General (upper/lower) ARill	ARill n=18				Median 4 Range (1-21)		
Rama et al (2013)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Episodes of upper ARinf n=31 in 19 athletes				6.7 ± 0.4		

Sawczuk et al (2020)	Self-reported symptoms only	Suspected ARinf	Upper ARinf	Upper ARinf episodes n=45				17 ± 18		
Schwellnus et al (2012)[a]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	General (upper/lower) ARinf	All ARinf n=98	Estimated time loss ARinf n=18 (18/98) 18.4% of all ARinf					
Schwellnus et al (2012)[b]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARill/ARinf	Upper ARill n=72	Upper ARinf n=13 (13/72) 18.1% of upper ARill					
Soligard et al (2017)	Physician (diagnosis by history and clinical examination)	Undiagnosed ARill	General (upper/lower) ARill	All ARill n=292	ARill n=54 (54/292) 18.5% of all ARill					
Somerville et al (2019)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf n=12				Average 12.3		
Somerville et al (2019)[a]	Self-reported symptoms with checklist and algorithm	Suspected ARinf	Upper ARinf	Number of subjects with ARinf in cohort 2 n=8, cohort 3				Mean upper ARinf duration per 1000 non-illness days		

	to diagnose infections			n=17, amateurs n=6				59.6 ± 183.2 (cohort 2) 522.1 ± 1138.8 (cohort 3) 64.3 ± 173.9 (amateurs)		
Somerville et al (2019)[b]	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Number of subject with ARinf in professional cohort n=12				Mean Upper ARinf duration per 1000 non-illness days 32.6 ± 59.7 (professionals)		
Spence et al (2007)[a]	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	All athletes confirmed ARinf n=9				9.6 ± 2.4		Rhinovirus most common pathogen isolated. Symptom and functional impairment severity scores were higher in subjects with an infectious pathogen episode, particularly on illness days 3–4

Spence et al (2007)[b]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	All athletes suspected upper ARinf n=19				6.5 ± 3.2		
Steffen et al (2019)	Physician (diagnosis by history and clinical examination)	Undiagnosed ARill	General (upper/lower) ARill	All ARill n=168	n=37 (37/168) 22% of ARill					Time loss ARill n=37, all illness time loss n=66 (56.1% of all time loss illness)
Stephenson et al (2019)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Upper ARinf	Upper ARinf n=22						During 50% of upper ARinf episodes, athletes had to reduce or suspend training
Svendsen et al (2016)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	General (upper/lower) ARinf	All ARinf n=410				5 ± 4		
Tiollier et al (2005)[a]	Physician (diagnosis by history and	Suspected ARinf	Upper ARinf	Upper ARinf episodes n=16 (upper ARinf symptoms				7.6 ± 1.2 (Mean ± SEM)		

	clinical examination)			recorded n=30: rhinopharyngitis n=12/30 (40%)						
Tiollier et al (2005)[a]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf (tonsillitis) n=5/30 (17%)				8.2 ± 3.8 (Mean ± SEM)		
Tiollier et al (2005)[a]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf (sinusitis) n=4/30 (13%)				10.7 ± 4.8 (Mean ± SEM)		
Tiollier et al (2005)[a]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Upper ARinf	Upper ARinf (otitis media) n=3/30 (10%)				4.3 ± 0.9 (Mean ± SEM)		
Tiollier et al (2005)[b]	Physician (diagnosis by history and clinical examination)	Suspected ARinf	Lower ARinf	Lower ARinf (bronchitis) n=6/30 (20%)				7.8 ± 2.3 (Mean ± SEM)		
Valtonen et al (2019)	Physician diagnosis including pathology confirmed	Confirmed ARinf	Upper ARinf	Upper ARinf (athletes with symptoms of "common cold") n=20				8.3 ± 7.8		Only one athlete lost competition on 1 day due to a

	(PCR/culture/ serology)									respiratory infection
Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	Coronavirus 229E n=2				13.5 ± 16.3		
Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	Influenza B n=1				7.0		
Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	Respiratory syncytial virus (RSV) A n=4				8.7 ± 3.2		
Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	UpperARinf	Rhinovirus n=1				2.0		

Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	Metapneumo virus n=4				4.0 ± 1.7		
Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	Coronavirus NL63 n=1				3.0		
Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	Coronavirus OC43 n=2				18.0 ± 11.3		
Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	Respiratory syncytial virus (RSV) B n=1				7.0		

Valtonen et al (2019)	Physician diagnosis including pathology confirmed (PCR/culture/ serology)	Confirmed ARinf	Upper ARinf	lnfluenza A n=1				3.0		
West et al (2011)	Self-reported symptoms with checklist and algorithm to diagnose infections	Suspected ARinf	Lower ARinf					7.4 ± 10.3 (males) 5.1 ± 14.7 (females)		

* Values are mean ± standard deviation (SD) unless stated differently
ARill, acute respiratory illness; ARinf, acute respiratory infection

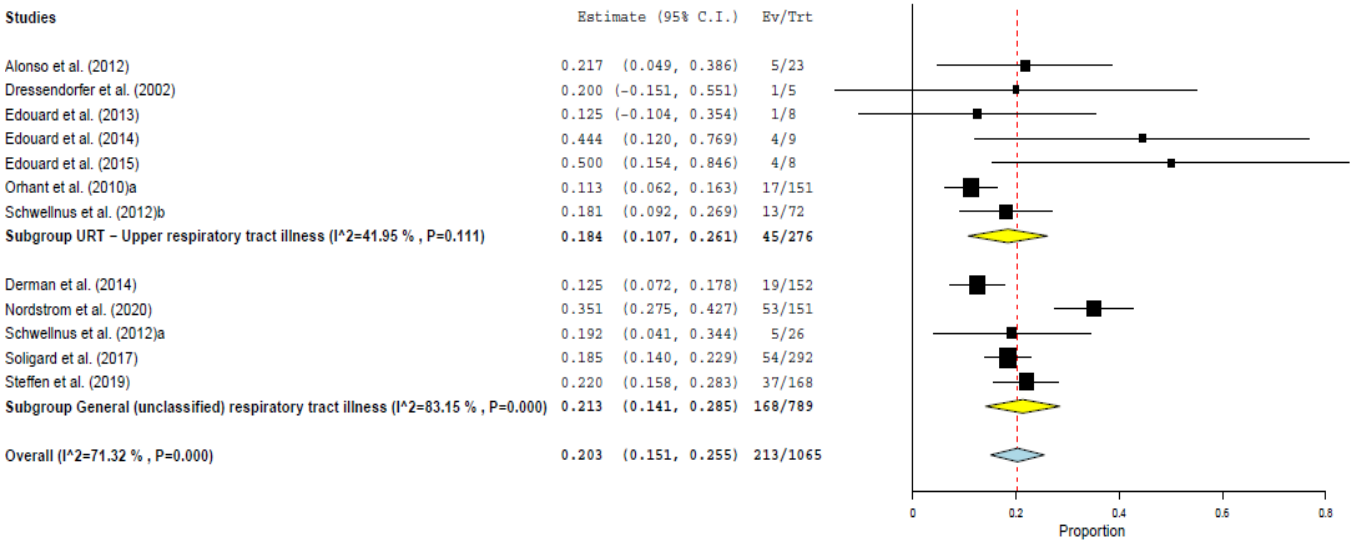
Online supplementary table C: Modified Downs and Black score and Oxford Level of Evidence

Author(s), Year	Modified Downs and Black (score out of 13)	Oxford Level of Evidence
Alonso et al (2012)	12	2b
Bjørneboe et al (2016)	11	1b
Chesson et al (2020)	10	1b
Cox et al (2010)	11	1b
Cox et al (2010)[a]	11	1b
Cox et al (2008)	10	2b
Cox et al (2004)	10	1b
Cunniffe et al (2011)	11	2b
Da Boit et al (2015)	11	1b
Davison et al (2020)	10	2b
Derman et al (2019)	12	2b
Derman et al (2014)	12	2b
Dressendorfer et al (2002)	9	2b
Edouard et al (2015)	13	2b
Edouard et al (2014)	12	2b
Edouard et al (2013)	12	2b
Fahlman and Engels (2005)	12	2b
Fricker et al (2005)	10	2b
Furusawa et al (2007)	9	3b
Gleeson et al (2012)[a]	10	2b
Gleeson et al (2011)	10	1b

Hall et al (2007)	10	1b
Hanstad et al (2011)	12	2b
Haywood et al (2014)	10	1b
He et al (2014)	10	1b
He et al (2013)[a]	11	1b
He et al (2013)[b]	11	2b
Henson et al (2008)	10	1b
Ihalainen et al (2015)	10	2b
Kekkonen et al (2007)	12	1b
Laaksi et al (2007)	12	1b
McFarlin et al (2013)	10	1b
Michalickova et al (2016)	9	1b
Nehlsen-Cannarella et al (2000)	11	2b
Nieman et al 2008	7	2b
Nordstrøm et al (2020)	12	2b
Orhant et al (2010)	8	2b
Orysiak et al (2017)	11	2b
Pacque et al (2007)	12	2b
Peters et al (2004)	10	2b
Pyne et al (2001)	12	2b
Rama et al (2013)	10	3b
Sawczuk et al (2020)	10	2b
Schwellnus et al (2012)	10	2b
Soligard et al (2017)	12	2b
Somerville et al (2019)	11	2b
Somerville et al (2019)[a]	10	2b
Spence et al (2007)	10	1b
Steffen et al (2019)	11	2b

Stephenson et al (2019)	10	3b
Svendsen et al (2016)	11	2b

Online supplementary figure 1: Frequency (%) time loss ARill by anatomical classification: Upper ARill vs. General (upper/lower) ARill

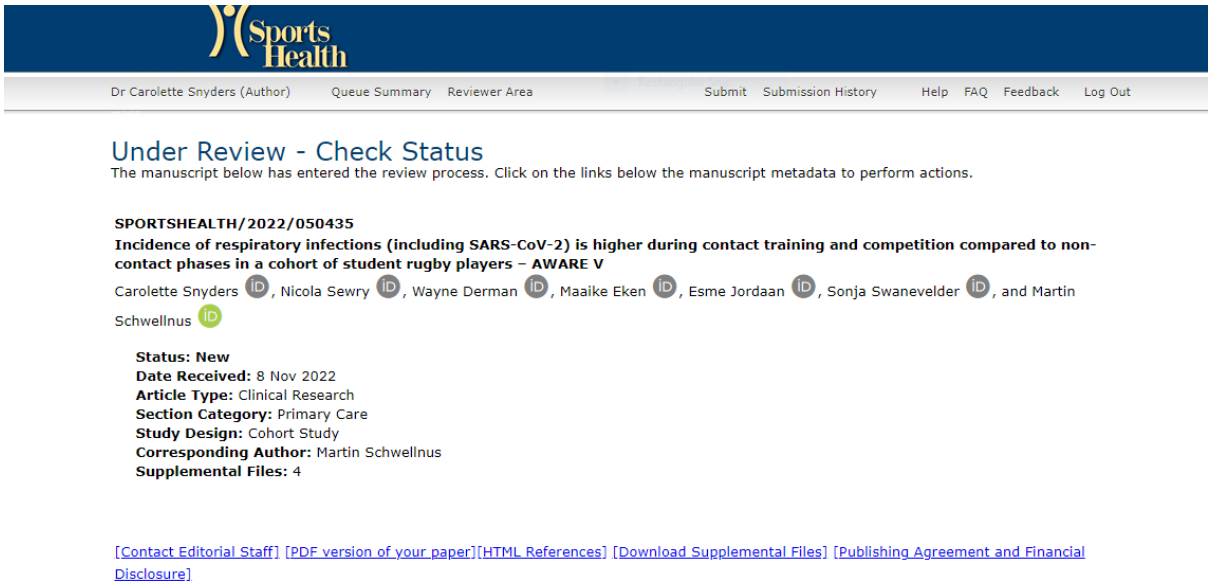


CHAPTER 4: Supplementary material

Incidence of respiratory infections (including SARS-CoV-2) is higher during contact training and competition compared to non-contact phases in a cohort of student rugby players – AWARE V

Manuscript submitted to Sport Health on 8 November 2022

Currently under review



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SPORTSHEALTH/2022/050435

Incidence of respiratory infections (including SARS-CoV-2) is higher during contact training and competition compared to non-contact phases in a cohort of student rugby players – AWARE V

Carolette Snyders, Nicola Sewry, Wayne Derman, Maaike Eken, Esme Jordaan, Sonja Swanevelder, and Martin Schwellnus

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Section Category: Primary Care
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Corresponding Author: Martin Schwellnus
Supplemental Files: 4

[Contact Editorial Staff] [PDF version of your paper][HTML References] [Download Supplemental Files] [Publishing Agreement and Financial Disclosure]

Supplementary Table A: Calculation of player days for each team during the four different phases for All ARinf

University		Phase 1 Individual			Phase 2 Non-contact			Phase 3 Contact			Phase 4 Competition		
	Team size	Nr inf	Days	Player days	Nr inf	Days	Player days	Nr inf	Days	Player days	Nr inf	Days	Player days[#]
1	23	0	214	4922	0	61	1403	1	66	1518	2	#	651
2	29	5	275	7975	0	31	899	0	63	1827	1	#	113
3	15	1	313	4695	0	22	330	2	39	585	0	#	124
4	17	1	306	5202	0	28	476	0	23	391	0	#	236
5	24	3	214	5136	1	30	720	4	102	2448	3	#	879
6	24	1	214	5136	2	30	720	0	102	2448	1	#	704
7	30	0	214	6420	0	30	900	3	109	3270	0	#	928
8	6	0	214	1284	0	30	180	1	102	612	0	#	176
9	21	1	275	5775	0	31	651	1	70	1470	0	#	46
10	17	1	306	5202	0	6	102	0	40	680	0	#	365
11	23	0	307	7061	0	22	506	0	28	644	0	#	373
12	14	0	313	4382	0	13	182	0	49	686	0	#	32
13	7	0	306	2142	0	28	196	0	45	315	0	#	49
14	25	0	275	6875	0	28	700	0	73	1825	0	#	27
15	20	0	320	6400	0	13	260	0	24	480	0	#	394
16	17	0	306	5202	0	20	340	0	21	357	0	#	340
17	7	0	275	1925	0	31	217	0	26	182	0	#	486
	319	**13**		**85734**	**3**		**8782**	**12**		**19738**	**7**		**5923**
		Number of infections = 16 Non-contact players days = 94 516						**Number of infections = 19 Contact player days = 25 661**					

Two players in 'Other ARinf' group did not specify when they were ill, and thus could not be allocated to a phase
Nr inf, number of infections; ARinf, acute respiratory infection
#Missing days =12 196

Supplementary Table B: Duration of specific symptoms during the acute phase of respiratory infections for All ARinf, SARS-CoV-2 and Other ARinf

Symptom duration	All ARinf Median days (Q1; Q3) n=33	SARS-CoV-2 Median days (Q1; Q3) n=24[#]	Other ARinf Median days (Q1; Q3) n=9
Nose and Throat			
Sore/scratchy throat	3 (3;4)	4 (3;4)	-
Hoarseness	-	-	-
Blocked/plugged nose	3 (2;5)	3.5 (2;6)	2.5 (2;5)
Runny nose	2.5 (2;4)	2 (2;4)	3 (2;5)
Sinus pressure	5 (2;7)	4 (2;9)	-
Sneezing	3.5 (2.5;5.5)	-	4 (2;7)
Altered/loss sense of smell	7 (4;52.5)	7 (5;44)	31.5 (2;61)
Altered/loss sense of taste	5.5 (3;16)	6 (5;16)	-
Chest and Neck			
Dry cough	4 (3.5;6)	4 (4;6)	4 (3;6)
Wet cough	4 (2;6)	3 (2;5)	-
Difficulty in breathing	4 (2;5)	3.5 (1.5;17.5)	-
Fast breathing/ shortness of breath	7.5 (5-10)	7.5 (5;10)	-
Chest pain/pressure	21.5 (3;40)	21.5 (3;40)	-
Chest tightness	3 (2;5)	3.5 (1.5;17.5)	-
Headache	3 (2.5;3.5)	3 (2;3)	-
Red/watery/ scratchy eyes	-	-	-
Whole Body			
Fever	3 (2;4)	2 (2;3)	4.5 (4;5)
Chills	3 (1;3)	2 (1;3)	-
Excessive fatigue	4 (4;5)	4 (3;7)	4.5 (4;5)
General muscle aches and pains	4 (2;5)	3 (2;5.5)	-
Skin rash	-	-	-
Abdominal pain	-	-	-
Nausea	3 (3;4)	-	-
Vomiting	-	-	-
Diarrhoea	4 (2;7)	4 (4;7)	2.5 (2;3)
Loss of appetite	5 (3;7)	5 (3;7)	-

Asymptomatic SARS-CoV-2 players were excluded (n=4)
-Numbers were too few to calculate quadrants (Q1 and Q3)
ARinf, acute respiratory infection

Supplementary Table C: Severity of specific symptoms during the acute phase of respiratory infections for All ARinf, SARS-CoV-2 and Other ARinf

Symptom Severity	All ARinf n=33				SARS-CoV-2 n=24[#]				Other ARinf n=9			
	Mild		Moderate/ Severe		Mild		Moderate/ Severe		Mild		Moderate/ severe	
	n	%	n	%	n	%	n	%	n	%	n	%
Nose and Throat												
Sore/scratchy throat	8	24.2	6	18.2	3	12.5	6	25.0	5	55.6	0	
Hoarseness	0		0		0		0		0		0	
Blocked/plugged nose	9	27.3	7	21.2	4	16.7	6	25.0	5	55.6	1	11.1
Runny nose	5	15.2	3	9.1	3	12.5	2	8.3	2	22.2	1	11.1
Sinus pressure	3	9.1	6	18.2	3	12.5	4	16.7	0		2	22.2
Sneezing	3	9.1	1	3.0	1	4.2	0		2	22.2	1	11.1
Altered/loss sense of smell	3	9.1	9	27.3	3	12.5	7	29.2	0		2	22.2
Altered/loss sense of taste	3	9.1	7	21.2	3	12.5	6	25.0	0		1	11.1
Chest and Neck												
Dry cough	2	6.1	6	18.2	1	4.2	4	16.7	1	11.1	2	22.2
Wet cough	4	12.1	2	6.1	3	12.5	2	8.3	1	11.1	0	
Difficulty in breathing	2	6.1	3	9.1	2	8.3	2	8.3	0		1	11.1
Fast breathing/shortness of breath	1	3.0	1	3.0	1	4.2	1	4.2	0		0	
Chest pain	0		2	6.1	0		2	8.3	0		0	
Chest tightness	3	9.1	2	6.1	2	8.3	2	8.3	1	11.1	0	
Headache	3	9.1	5	15.2	3	12.5	4	16.7	0		1	11.1
Red/watery/scratchy eyes	0		0		0		0		0		0	
Whole Body												
Fever	3	9.1	2	6.1	2	8.3	1	4.2	1	11.1	1	11.1
Chills	2	6.1	1	3.0	1	4.2	1	4.2	1	11.1	0	
Excessive fatigue	4	12.1	9	27.3	3	12.5	8	33.3	1	11.1	1	11.1
Muscle aches/pains	3	9.1	2	6.1	3	12.5	1	4.2	0		1	11.1
Skin rash	0		0		0		0		0		0	
Abdominal pain	0		0		0		0		0		0	
Nausea	0		3	9.1	0		1	4.2	0		2	22.2
Vomiting	0		1	3.0	0		0		0		1	11.1
Diarrhoea	4	12.1	3	9.1	3	12.5	2	8.3	1	11.1	1	11.1
Loss of Appetite	1	3.0	1	3.0	1	4.2	1	4.2	0		0	

#Asymptomatic SARS-CoV-2 players were excluded (n=4)
Those who did not report the symptom, had a severity of 0, and make up the rest, to 100%
ARinf, acute respiratory infection

CHAPTER 5: Supplementary material

Symptom number and reduced pre-infection training predict prolonged return to training after SARS-CoV-2 in athletes: AWARE IV

AMERICAN COLLEGE of SPORTS MEDICINE
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Symptom Number and Reduced Pre-infection Training Predict Prolonged Return to Training after SARS-CoV-2 in Athletes: AWARE IV

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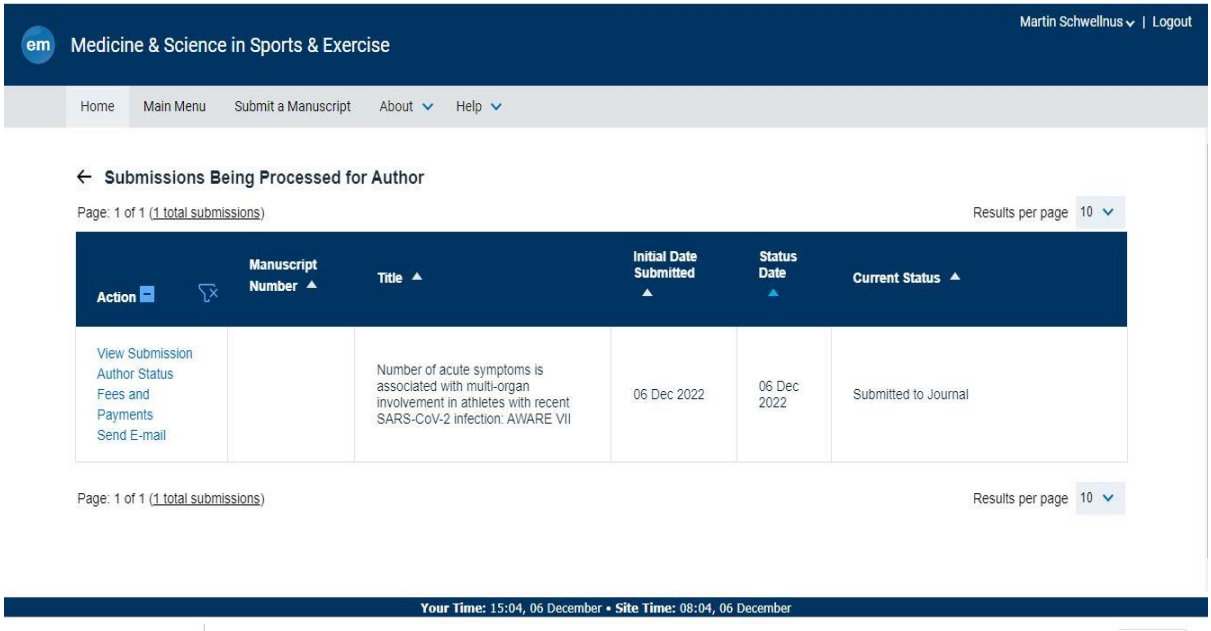
Supplementary Digital Content 1: The number, duration and severity of symptoms by anatomical region and specific symptoms in participants (n=207)

Symptoms	Number		Duration	Severity*			
				Mild		Moderate/ Severe	
	n	% (95% CI)	Median (days;Q1-Q3)[#]	n	%	n	%
Nose and Throat							
Sore/Scratchy Throat	102	49.3 (42.4-56.1)	4.5 (4-5)	60	29.0	42	20.3
Hoarseness	26	12.6 (8.0-17.1)	4.5 (3-6)	8[a]	4.0	9[a]	4.6
Blocked/plugged nose	105	50.7 (43.9-57.6)	5 (5-7)	46	22.2	59	28.5
Runny nose	45	21.7 (16.1-27.4)	4 (4-5)	31	15.0	14	6.8
Sinus Pressure	65	31.4 (25.0-37.8)	6 (4-7)	22[b]	10.7	42[b]	20.4
Sneezing	32	15.5 (10.5-20.4)	4 (3-5)	22	10.6	10	4.8
Altered/loss sense of smell	111	53.6 (46.8-60.5)	7 (6-10)	25	12.1	86	41.6
Altered/loss sense of taste	98	47.3 (40.5-54.2)	7 (6-9)	24	11.6	74	35.8
Chest and Neck							
Dry Cough	75	36.2 (26.9-42.8)	6 (5-7)	42	20.3	33	15.9
Wet Cough	47	22.7 (17.0-28.5)	5 (3-7)	27	13.0	20	9.7
Difficulty in breathing	46	22.2 (16.5-27.9)	5 (4-7)	24	11.6	22	10.7
Fast breathing/ shortness of breath	46	22.2 (16.5-27.9)	7 (5-10)	19	9.2	27	13.0
Chest pain	42	20.3 (14.8-25.8)	5 (3-7)	14	6.8	28	13.5
Chest tightness	42	20.3 (14.8-25.8)	5 (4-7)	18	8.7	24	11.6
Headache	118	57.0 (50.2-63.8)	4 (4-5)	40	19.3	78	37.7
Red/watery/scratchy eyes	27	13.0 (8.4-17.7)	7 (5-9)	15	7.3	12	5.8
Whole Body							
Fever	73	35.3 (28.7-41.8)	3 (2-4)	27	13.0	46	22.2
Chills	43	20.8 (15.2-26.3)	3 (2-3)	13	6.3	30	14.5
Excessive fatigue	119	57.5 (50.7-64.3)	7 (6-8)	30	14.5	89	43.0
Muscle aches/pains	88	42.5 (35.7-49.3)	5 (4-6)	28	13.5	60	29.0
Skin rash [^]	6	2.9 (0.6-5.2)	3.5 (1-14)	2	-	4	-
Abdominal pain	19	9.2 (5.2-13.1)	3 (2-4)	10	4.8	9	4.4
Nausea	27	13.0 (8.4-17.7)	4 (3-5)	12	5.8	15	7.3
Vomiting [^]	1	-	-	1	-	0	-
Diarrhoea	19	9.2 (5.2-13.1)	3 (2-4)	6	2.9	13	6.3
Loss of Appetite	63	30.4 (24.1-36.8)	7 (5-7)	21	10.1	42	20.3

[*] Those who did not report the symptom, had a severity of 0, and make up the rest to 100%
- Q1 25th percentile, Q3 75th percentile
[^] Numbers were too small for further analyses
Number of participants with missing data: a=9, b=1

CHAPTER 6: Supplementary material



Supplementary File A: Standardized clinical assessment of an athlete with acute

SYMPTOM ASSESSMENT AND PHYSICAL EXAMINATION FORM

FIRST ASSESSMENT

Date:

Name of participant: Age:

Sporting code: Sex: ☐Male Female

ACUTE PHASE ONSET AND TESTING

Date onset of symptoms:

COVID-19 / Other Pathogen Test ☐No ☐Yes If yes specify date:

Laboratory test: ☐None ☐PCR ☐Antigen ☐Antibodies

Pathogen identified: ☐No ☐Yes If yes specify:

Have you started training again? ☐No ☐Yes If yes, specify date:

Recent illness (COVID-19 / other infection excluded)? ☐No ☐Yes If yes, specify date:

Recent injury? ☐No ☐Yes If yes, specify date:

If yes to recent illness or injury then describe ☐illness ☐injury:

MEDICATION USE IN ACUTE PHASE:

- Antibiotics ☐No ☐Yes Specify:
- Antivirals ☐No ☐Yes Specify:
- Nose sprays ☐No ☐Yes Specify:
- Throat sprays ☐No ☐Yes Specify:
- Pain medication ☐No ☐Yes Specify:
- Fever medication ☐No ☐Yes Specify:
- Cough syrup/medication ☐No ☐Yes Specify:
- Inhalers for chest tightness ☐No ☐Yes Specify:
- Decongestants ☐No ☐Yes Specify:
- Anti-nausea medication ☐No ☐Yes Specify:

- Anti-diarrhoea medication ☐No ☐Yes Specify:
- Abdominal cramps medication ☐No ☐Yes Specify:
- Mucolytics ☐No ☐Yes Specify:
- Anticoagulants ☐No ☐Yes Specify:
- Vitamins ☐No ☐Yes Specify:
- Immune boosters ☐No ☐Yes Specify:
- Supplement ☐No ☐Yes Specify:
- Probiotics ☐No ☐Yes Specify:
- Other ☐No ☐Yes Specify:

ACUTE PHASE SYMPTOMS (similar to REDCap)

Nose and throat

- Sore/scratchy throat ☐No ☐Yes
- Hoarseness ☐No ☐Yes
- Blocked/plugged nose ☐No ☐Yes
- Runny nose ☐No ☐Yes
- Sinus pressure ☐No ☐Yes
- Sneezing ☐No ☐Yes
- Altered/loss of smell ☐No ☐Yes
- Altered/loss of taste ☐No ☐Yes

Total number of nose and throat symptoms: ☐

Chest and neck

- Dry cough ☐No ☐Yes
- Wet cough i.e. sputum/mucous ☐No ☐Yes
- Difficulty in breathing (dyspnoea) ☐No ☐Yes
- Fast breathing or shortness of breath (tachypnea) ☐No ☐Yes
- Chest pain/discomfort/pressure ☐No ☐Yes
- Chest tightness/wheezing ☐No ☐Yes

- Headache ☐No ☐Yes
- Red, watery eye ☐No ☐Yes

Total number of chest and neck symptoms: ☐

Whole body/systemic

- Fever ☐No ☐Yes
- Chills ☐No ☐Yes
- Excessive tiredness ☐No ☐Yes
- Myalgia ☐No ☐Yes
- Skin rash/discolouration tips fingers or toes ☐No ☐Yes
- Abdominal (stomach) pain ☐No ☐Yes
- Nausea ☐No ☐Yes
- Vomiting ☐No ☐Yes
- Diarrhoea ☐No ☐Yes
- Loss of appetite ☐No ☐Yes

Total number of whole body: ☐

Total number of acute phase symptoms (nose/throat + chest/neck + whole body) : ☐

Residual symptoms (currently present):

Nose and throat

- Sore/scratchy throat ☐No ☐Yes
- Hoarseness ☐No ☐Yes
- Blocked/plugged nose ☐No ☐Yes
- Runny nose ☐No ☐Yes
- Sinus pressure ☐No ☐Yes
- Sneezing ☐No ☐Yes
- Altered/loss of smell ☐No ☐Yes
- Altered/loss of taste ☐No ☐Yes

Chest and neck

- Dry cough ☐No ☐Yes
- Wet cough i.e. sputum/mucous ☐No ☐Yes
- Difficulty in breathing (dyspnoea) ☐No ☐Yes
- Fast breathing or shortness of breath (tachypnea) ☐No ☐Yes
- Chest pain/discomfort/pressure ☐No ☐Yes
- Chest tightness/wheezing ☐No ☐Yes
- Headache ☐No ☐Yes
- Red, watery eye ☐No ☐Yes

Whole body/systemic

- Fever ☐No ☐Yes
- Chills ☐No ☐Yes
- Excessive tiredness ☐No ☐Yes
- Myalgia ☐No ☐Yes
- Skin rash/discolouration tips fingers or toes ☐No ☐Yes
- Abdominal (stomach) pain ☐No ☐Yes
- Nausea ☐No ☐Yes
- Vomiting ☐No ☐Yes
- Diarrhoea ☐No ☐Yes
- Loss of appetite ☐No ☐Yes

Additional physician notes:

GENERAL MEDICAL EXAMINATION BY ORGAN SYSTEM

Vital Physical Signs

- Blood pressure
- Pulse ☐Regular ☐Irregular
- Respiratory rate

- Temp (right tympanic)
- Oxygen saturation (%)

General physical signs

- Cyanosis ☐Absent ☐Present
- Pallor ☐Absent ☐Present
- Clubbing ☐Absent ☐Present
- Jaundice ☐Absent ☐Present
- Pedal Oedema ☐Absent ☐Present
- Respiratory distress ☐Absent ☐Present

Cardiovascular System

- Rhythm ☐Normal ☐Abnormal Specify:
- Apex beat ☐Normal ☐Abnormal
- Thrills ☐Absent ☐Present
- Murmurs ☐Absent ☐Present
- If present: Murmur grade ☐1 ☐2 ☐3 ☐4 ☐5 ☐6

  ***Grade I**: faintest murmur (softer than S1 and S2); **Grade II**: faint murmur but has the same intensity as S1 and S2; **Grade III**: louder than S1 and S2 without a palpable thrill; **Grade IV**: loud and associated with a palpable thrill; **Grade V**: very loud with a thrill; **Grade VI**: loudest (can be heard without a stethoscope)*
- Murmur type ☐Diastolic ☐Systolic
- Elevated JVP ☐Absent ☐Present
- DVT ☐No ☐Yes

Myocarditis/pericarditis checklist:

- Pericardial rub ☐No ☐Yes
- Chest pain ☐No ☐Yes
- Short of breath (prominent when lying down in pericarditis) ☐No ☐Yes
- Ankle oedema ☐No ☐Yes
- Pulmonary oedema ☐No ☐Yes
- Tachycardia ☐No ☐Yes
- Arrhythmias ☐No ☐Yes

- Fatigue ☐No ☐Yes
- Dysphagia (pericarditis) ☐No ☐Yes

Respiratory System

- Chest wall ☐Normal ☐Abnormal Specify:
- Breathing sounds ☐Normal ☐Abnormal Specify:

Abdominal

- Organomegaly ☐No ☐Yes Specify:
- Tenderness No ☐Yes Specify:

Neurological

- Neck stiffness No ☐Yes
- Power ☐Deferred ☐Normal ☐Abnormal Specify:
- Sensation ☐Deferred ☐Normal ☐Abnormal Specify:
- Reflexes ☐Deferred ☐Normal ☐Abnormal Specify:
- Balance ☐Deferred ☐Normal ☐Abnormal Specify:

Meningitis checklist

Headache ☐No ☐Yes
Nausea/vomiting ☐No ☐Yes
Neck stiffness ☐No ☐Yes
Photophobia ☐No ☐Yes
Confusion/difficulty to concentrate ☐No ☐Yes
Speech disturbances ☐No ☐Yes
Behavioural changes ☐No ☐Yes
Meningococcal skin rash ☐No ☐Yes

Dermatological

General skin ☐Deferred ☐Normal ☐Abnormal Specify:

Eye

R conjunctivitis ☐No ☐Yes
L conjunctivitis ☐No ☐Yes

Pupil reaction ☐Normal ☐Abnormal

Ear

R Auditory meatus ☐Normal ☐Abnormal Specify:

L Auditory meatus ☐Normal ☐Abnormal Specify:

R Tympanic membrane ☐Normal ☐Abnormal Specify:

L Tympanic membrane ☐Normal ☐Abnormal Specify:

Nose and sinuses

R Nostrils ☐Normal ☐Abnormal Specify:

L Nostrils ☐Normal ☐Abnormal Specify:

Septum ☐Normal ☐Abnormal Specify:

R sinuses ☐Normal ☐Abnormal Specify:

L sinuses ☐Normal ☐Abnormal Specify:

Oral cavity and throat

Palate ☐Normal ☐Abnormal Specify:

Uvula ☐Normal ☐Abnormal Specify:

R tonsillar area ☐Normal ☐Abnormal Specify:

L Tonsillar area ☐Normal ☐Abnormal Specify:

Posterior pharyngeal wall ☐Normal ☐Abnormal Specify:

Thyroid

Thyroid palpation ☐Normal ☐Abnormal Specify:

Lymph nodes

R Cervical ☐Non-palpable ☐ Palpable ☐Non-tender ☐Tender
L Cervical ☐Non-palpable ☐ Palpable ☐Non-tender ☐Tender
R Axilla ☐Non-palpable ☐ Palpable ☐Non-tender ☐Tender
L Axilla ☐Non-palpable ☐ Palpable ☐Non-tender ☐Tender
R Groin ☐Non-palpable ☐ Palpable ☐Non-tender ☐Tender
L Groin ☐Non-palpable ☐ Palpable ☐Non-tender ☐Tender

Additional clinical notes

Medication prescribed

Special investigations
Blood tests
☐ FBC
☐ CRP
☐ UKE
☐ CK
☐ Trop T
☐ AST
☐ ALT
☐ COVID-19 Antibodies

Imaging ☐No ☐Yes Specify:

Exercise advise

☐ No exercise
☐ Return to training: Date

Follow up consult appointment: Date

Supplementary Table A: Demographics, sport participation and history of co-morbidities for study participants (n=95)

Variables	All (n=95)
Demographics	
Age (years) (mean) (SD)	25 (7.1)
Sex	
Male n (%)	60 (63.2)
Female n (%)	35 (36.8)
BMI (mean) (SD)	24.4 (3.9)
Sport participation	
Level of participation	
Professional n (%)	44 (46.3)
Amateur n (%)	51 (53.7)
Type of sport	
Endurance [#] n (%)	43 (45.3)
Mixed [α] (including skills [β] n=2 and power [¥] n=7) n (%)	52 (54.7)
History of co-morbidities	
Any co-morbidity n (%)	**49 (51.6)**
Number of co-morbidities per participant (mean, SD)	1.1 (1.5)
Individual co-morbidities by organ system	
Cardiovascular n (%)	8 (8.4)
Risk factors cardiovascular disease n (%) [a]	11 (11.7)
Respiratory n (%)	25 (26.3)
Nervous system n (%)	5 (5.3)
Psychological disorders n (%)	9 (9.5)
Gastrointestinal n (%)	11 (11.6)
Metabolic n (%)	3 (3.2)
Renal or bladder n (%)	1 (1.1)
Immunological/haematological n (%)	5 (5.3)
History of growths/cancer n (%)	2 (2.1)
Allergies (yes) n (%)	22 (23.2)

[#] Cycling, mid/long distance swimming/running, triathlon
[α] Rugby, field hockey, soccer, tennis
[β] Golf
[¥] Short distance running, shot put, javelin, discus, gymnastics, judo
Missing data on participants: a=1

Supplementary Table B: The frequency (% athlete assessments) of multi-organ involvement (residual symptoms or abnormal clinical signs/laboratory investigations) among athletes assessed 10-28 days after acute SARS-CoV-2 infection (individual variables)

Variables	All n (%)
SECTION B1 (n=96)	
Cardiovascular	
Chest pain [a]	12 (12.6)
Racing heart	22 (22.9)
Irregular heartbeats	4 (4.2)
Respiratory	
Upper respiratory	
Sore throat	11 (11.5)
Hoarseness	6 (6.3)
Blocked nose	19 (19.8)
Runny nose	11 (11.5)
Sinus pressure	19 (19.8)
Sneezing	9 (9.4)
Other [β]	5 (5.2)
Lower respiratory	
Dry cough	22 (22.9)
Wet cough	11 (11.5)
Dyspnoea	15 (15.6)
Shortness of breath	32 (33.3)
Chest tightness	15 (15.6)
Other (trachea feels constricted)	1 (1.0)
Neurological	
Headache [a]	18 (19.0)
Excessive fatigue	22 (22.9)
Dizziness	8 (8.3)
Nerve tingling [b]	1 (1.1)
Balance/coordination problems [a]	4 (4.2)
Altered/loss sense of smell	26 (27.1)
Altered/loss sense of taste	23 (24.0)

Other [φ]	12 (12.5)
Gastrointestinal	
Abdominal pain	4 (4.2)
Nausea	4 (4.2)
Vomiting	0
Diarrhoea [a]	2 (2.1)
Loss of appetite	7 (7.3)
Musculoskeletal	
Muscle	10 (10.4)
Myalgia	4 (4.2)
Muscles cramps	1 (1.0)
Muscle stiffness	7 (7.3)
Joint	2 (2.1)
Joint pains	2 (2.1)
Ocular	
Red scratchy eyes [b]	4 (4.3)
Other (dry eyes)	1 (1.0)
Systemic	
Fever/Chills	0
SECTION B2 (n=96)	
Cardiovascular	
Resting HR >100 bpm, SBP >200 mm Hg,[c] pericardial rub [b], raised JVP [c], DVT [c]	0
Respiratory	
Oxygen saturation <90%	0
Upper respiratory	
Tympanic membrane erythema/bulging/absence light cone [c]	19 (20.4)
Sinus tenderness [b]	14 (14.9)
Posterior pharynx erythema/enanthema/sores [d]	3 (3.2)
Tonsillar erythema/sores	
Lower respiratory	
Abnormal breath sounds	0
Neurological	
Neck stiffness	0

Gastrointestinal	
Abdominal tenderness (epigastric, RUQ, LUQ, periumbilical, right and left iliac fossa) [e]	9 (9.9)
Skin	
Skin rash/discolouration	2 (2.1)
Ocular	
Conjunctivitis [f]	3 (3.2)
Systemic	
Fever	0
SECTION B3 (n=96)	
Cardiovascular	
Electrocardiogram (ECG) (Any)	9 (9.4)
Resting ECG	2 (2.1)
Submaximal exercise ECG [a]	7 (7.5)
ECHO (Any) [a]	3 (3.2)
Decreased LVEF	0
LV wall motion abnormalities [a]	2 (2.1)
Pericardial effusion	0
Left ventricular dysfunction [a]	1 (1.1)
hs-TnT [b]	0
Respiratory	
Resting PFT [b]	6 (6.4)
FEV_1< LLN [b]	2 (2.1)
FVC< LLN [b]	3 (3.2)
FEV_1/FVC < LLN [b]	3 (3.2)
Gastrointestinal	
AST	16 (16.7)
ALT	14 (14.6)
Musculoskeletal	
Creatine kinase [d]	10 (10.8)
Immune/blood system	
WCC	6 (6.3)
Neutrophil count	7 (7.3)
Lymphocyte count (n=96)	0
CRP (n=95) [a]	1 (1.1)

SECTION B4 (n=65)	
Myocardial LGE	13 (20.0)
Pericardial LGE	8 (12.3)
Pericardial effusion 5-10 mm	7 (10.8)
Pericardial effusion >10mm	1 (1.5)
Decreased LVEF	3 (4.6)
Wall motion abnormalities	1 (1.5)
T1 mapping	1 (1.5)
T2 mapping	1 (1.5)
Myocarditis (Lake Louise criteria)	1 (1.5)

β Post nasal drip, bilateral earache, and 'blocked' ears
φ Sleep disturbances, feeling slow, mood swings, irritable, increased anxiety, 'brain fog', slight hearing loss, tires easily, lightheaded, forgetful
HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; mmHg, millimetre mercury; JVP, jugular venous pressure; DVT, deep vein thrombosis; RUQ, right upper quadrant; LUQ, left upper quadrant
ECHO, echocardiogram; LVEF, left ventricular ejection fraction; LV, left ventricle; LGE, late gadolinium enhancement; hs-Trop T, high-sensitivity Troponin T; PFT, pulmonary function test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; AST, aspartate transaminase; ALT, alanine transaminase; WCC, white cell count; CRP, C-reactive protein
Missing data on participants: a=1; b=2, c=6, d=3, e=5, f=15

Supplementary Table C: The frequency (% athlete assessments) of residual symptoms, abnormal clinical signs/laboratory investigations and cardiac magnetic resonance imaging for participants in three different subgroups based on total number of symptoms during the acute phase of the infection (individual variables)

Variables, n	Subgroup 1 (≤5 acute symptoms) (n=29)	Subgroup 2 (6-9 acute symptoms) (n=34)	Subgroup 3 (≥10 acute symptoms) (n=32)	p-value (2 vs. 1)	p-value (3 vs. 1)	p-value (All subgroups)
SECTION C1						
RESIDUAL SYMPTOMS [a] (n=96)						
Cardiovascular						
Chest pain	0	3 (9.1) [b]	9 (28.1)	-	-	-
Racing heart	1 (3.3)	10 (29.4)	11 (34.4)	-	-	-
Irregular heartbeats	0	1 (2.9)	3 (9.4)	-	-	-
Respiratory						
Upper respiratory						
Sore throat	2 (6.7)	3 (8.8)	-	-	-	-
Hoarseness	0	1 (2.9)	-	-	-	-
Blocked nose	4 (13.3)	3 (8.8)	12 (37.5)	-	-	-
Runny nose	2 (6.7)	3 (8.8)	6 (18.8)	-	-	-
Sinus pressure	3 (10.0)	7 (20.6)	9 (28.1)	0.415	0.135	0.212
Sneezing	4 (13.3)	3 (8.8)	2 (6.3)	-	-	-
Other [β]	1 (3.3)	1 (2.9)	3 (9.4)	-	-	-
Lower respiratory [c]						
Dry cough	3 (10.0)	9 (26.5)	10 (31.3)	0.17	0.078	0.119
Wet cough	0	5 (14.7)	6 (18.8)	-	-	-
Dyspnoea	1 (3.3)	4 (11.8)	10 (31.3)	-	-	-
Shortness of breath	7 (23.3)	12 (35.3)	13 (40.6)	0.442	0.236	0.357
Chest tightness	1 (3.3)	7 (20.6)	7 (21.9)	-	-	-
Other (trachea feels constricted)	0	1 (2.9)	0	-	-	-
Neurological						
Headache	2 (6.7)	6 (18.2) [b]	10 (31.3)	-	-	-
Excessive fatigue	1 (3.3)	9 (26.5)	12 (37.5)	-	-	-
Dizziness	0	3 (8.8)	5 (15.6)	-	-	-
Nerve tingling	0	0	1 (3.3) [a]	-	-	-
Balance/coordination problems	0	1 (2.9)	3 (9.7) [b]	-	-	-
Altered/loss sense of smell	9 (30.0)	5 (14.7)	12 (37.5)	0.241	0.724	0.105
Altered/loss sense of taste	7 (23.3)	5 (14.7)	11 (34.4)	0.574	0.499	0.186
Other [φ]	1 (3.3)	4 (11.8)	7 (21.9)	-	-	-
Gastrointestinal						
Abdominal pain	0	2 (5.9)	2 (6.3)	-	-	-

Nausea	1 (3.3)	0	3 (9.4)	-	-	-
Vomiting	0	0	0	-	-	-
Diarrhoea	1 (3.3)	1 (3.0) [b]	0	-	-	-
Loss of appetite	1 (3.3)	3 (8.8)	3 (9.4)	-	-	-
Musculoskeletal						
Muscle	0	3 (8.8)	7 (21.9)	-	-	-
Myalgia	0	0	4 (12.5)	-	-	-
Muscles cramps	0	1 (2.9)	0	-	-	-
Muscle stiffness	0	3 (8.8)	4 (12.5)	-	-	-
Joint	0	1 (2.9)	1 (3.1)	-	-	-
Joint pains	0	1 (2.9)	1 (3.1)	-	-	-
Ocular						
Red/scratchy eyes	0	3 (9.1) [b]	1 (3.2) [b]	-	-	-
Other (dry eyes)	0	0	1 (1.0)	-	-	-
Systemic						
Fever/Chills	0	0	0	-	-	-
SECTION C2						
ANY ABNORMAL CLINICAL SIGN [d] (n=96)						
Cardiovascular [e]						
Resting HR >100 bpm, SBP >200 mm Hg [f], pericardial rub [a], raised JVP [f], DVT [f]	0	0	0			
Respiratory						
Oxygen saturation <90%	0	0	0			
Upper respiratory [g]						
Tympanic membrane erythema/bulging/absence light cone	7 (24.1) [b]	5 (15.2) [b]	7 (22.6) [b]	0.567	1	0.653
Sinus tenderness	2 (6.7)	2 (5.9)	10 (33.3) [a]	-	-	-
Posterior pharynx erythema/enanthema/sores	0 [a]	1 (2.9)	2 (6.5) [b]	-	-	-
Tonsillar erythema/sores	0	0	0			
Lower respiratory						
Abnormal breath sounds	0	0	0			
Neurological						
Neck stiffness	0	0	0			
Gastrointestinal						
Abdominal tenderness (epigastric, RUQ, LUQ, periumbilical, right and left iliac fossa) [h]	0 [c]	3 (9.1) [b]	6 (19.4) [b]	-	-	-
Skin						
Skin rash/ discolouration	0	1 (2.9)	1 (3.1)	-	-	-
Ocular						
Conjunctivitis	0	2 (6.1) [h]	1 (3.2) [h]	-	-	-

Systemic						
Fever	0	0	0			
SECTION C3						
ANY ABNORMAL LABORATORY INVESTIGATION (n=96)						
Cardiovascular [#]						
Electrocardiogram (ECG) (Any)	3 (10.0)	4 (11.8)	2 (6.3)	0.734	1	0.739
Resting ECG	2 (6.7)	0	0	0.734	1	0.739
Submaximal exercise ECG [b]	1 (3.5) [b]	4 (11.8)	2 (6.3)	0.734	1	0.739
ECHO (Any)	2 (6.7)	1 (3.0) [b]	0	0.734	1	0.739
Decreased LVEF	0	0	0	0.734	1	0.739
LV wall motion abnormalities	1 (3.3)	1 (3.0) [b]	0	0.734	1	0.739
Pericardial effusion	0	0	0	-	-	-
Left ventricular dysfunction	1 (3.3)	0[b]	0	-	-	-
hs-TnT [a]	0	0	0	-	-	-
Respiratory						
Resting PFT	0	4 (12.1) [b]	2 (6.5) [b]	-	-	-
FEV_1< LLN	0	1 (3.0) [b]	1 (3.2) [b]	-	-	-
FVC< LLN	0	2 (6.1) [b]	1 (3.2) [b]	-	-	-
FEV_1/FVC < LLN	0	2 (6.1) [b]	1 (3.2) [b]	-	-	-
Gastrointestinal						
AST	4 (13.3)	4 (11.8)	8 (25.0)	1	0.402	0.299
ALT	2 (6.7)	3 (8.8)	9 (28.1)	-	-	-
Musculoskeletal						
Creatine kinase [c]	3 (10.0)	3 (9.4) [a]	4 (12.9) [b]	1	1	0.919
Immune/blood system						
WCC	2 (6.7)	2 (5.9)	2 (6.3)	-	-	-
Neutrophil count	4 (13.3)	1 (2.9)	2 (6.3)	-	-	-
Lymphocyte count (n=96)	0	0	0	-	-	-
CRP (n=95)	1 (3.3)	0 [b]	0	-	-	-
SECTION C4						
ANY ABMORNAL CMR (n=65)						
Myocardial LGE	1 (6.7)	6 (25.0)	6 (23.1)	-	-	-
Pericardial LGE	0	5 (20.8)	3 (11.5)	-	-	-
Pericardial effusion 5-10 mm	1 (6.7)	3 (12.5)	3 (11.5)	-	-	-
Pericardial effusion >10mm	0	1 (4.2)	0	-	-	-
Decreased LVEF	2 (13.3)	0	1 (3.9)	-	-	-
Wall motion abnormalities	0	0	1 (3.9)	-	-	-
T1 mapping	0	1 (4.2)	0	-	-	-
T2 mapping	0	1 (4.2)	0	-	-	-
Myocarditis (Lake Louise criteria)	0	1 (4.2)	0	-	-	-

- Numbers too small to test statistical significance

β Post nasal drip, bilateral earache, and 'blocked' ears

φ Sleep disturbances, feeling slow, mood swings, irritable, increased anxiety, 'brain fog', slight hearing loss, tires easily, lightheaded, forgetful

HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; mmHg, millimetre mercury; JVP, jugular venous pressure; DVT, deep vein thrombosis; RUQ, right upper quadrant; LUQ, left upper quadrant, ECHO, echocardiogram; LVEF, left ventricular ejection fraction; LV, left ventricle; CMR, cardiac magnetic resonance imaging, LGE, late gadolinium enhancement; hs-Trop T, high-sensitivity Troponin T; PFT, pulmonary function test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limit of normal; AST, aspartate transaminase; ALT, alanine transaminase; WCC, white cell count; CRP, C-reactive protein
Missing data on participants: a=2; b=1, c=3, d=15, e=7, f=6, g=9, h=5

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07-Dec-2022

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Supplementary table A: The number (%), duration (days) and severity (mild or moderate/severe) of specific symptoms and symptoms by anatomical region in all symptomatic assessments (n=79)

Symptoms (type)	Number		Duration	Severity #			
				Mild		Moderate/ Severe	
	n	%	Median (days) (IQR)	n	%	n	%
Nose and throat	**79**	**100**					
Sore/scratchy throat	47	59.5	4 (4;5)	28	35.4	19	24.1
Hoarseness	13	16.5	4 (2;7)	3	4.2	2	2.8
Blocked/plugged nose	52	65.8	6 (5;7)	29	36.7	23	29.1
Runny nose	21	26.6	5 (4;10)	11	13.9	10	12.7
Sinus pressure	39	49.4	5 (4;8)	12	15.2	27	34.2
Sneezing	10	12.7	4 (3;6)	7	8.9	3	3.8
Altered/loss sense of smell	45	57.0	8 (6;10)	9	11.4	36	45.6
Altered/loss sense of taste	40	50.6	7 (6;9)	8	10.1	32	40.5
Chest and neck	**68**	**86.1**					
Dry cough	28	35.4	8 (4;9)	16	20.3	12	15.2
Wet cough	33	41.8	5 (5;8)	14	17.7	19	24.1
Difficulty in breathing	18	22.8	5 (3;8)	11	13.9	7	8.9
Fast breathing/ shortness of breath	18	22.8	5 (3;7)	8	10.1	10	12.7
Chest pain	21	26.6	4 (2;6)	6	7.6	15	19.0
Chest tightness	14	17.7	6.5 (2;10)	8	10.1	6	7.6
Headache	47	59.5	4 (3;5)	13	16.5	34	43.0
Red/watery, scratchy/eyes	14	17.7	5 (4;9)	7	8.9	7	8.9
Whole body	**63**	**79.7**					
Fever	26	32.9	2.5 (2;3)	5	6.3	21	26.6
Chills	24	30.4	3 (2;3)	5	6.3	19	24.1
Excessive fatigue	49	62.0	7 (5;9)	7	8.9	42	53.2
Muscle aches/pains	41	51.9	4 (3;5)	16	20.3	25	31.7
Skin rash	1	1.3	-	-	-	-	-
Abdominal pain	8	10.1	4 (2;4)	4	5.1	4	5.1
Nausea	11	13.9	3 (2;5)	7	8.9	4	5.1
Vomiting	1	1.3	-	-	-	-	-
Diarrhoea	6	7.6	3 (1;10)	2	2.5	4	5.1
Loss of Appetite	22	27.9	4.5 (3;6)	8	10.1	14	17.7

Those who did not report the symptom, had a severity of 0, and make up the rest to 100
-Numbers too few to do calculation

Supplementary table B: The Hazard Ratio (95%CI) for return to full performance (RTFP) and the presence of symptoms during the acute phase of infection by anatomical region and specific symptoms (n=79) (Univariate model)

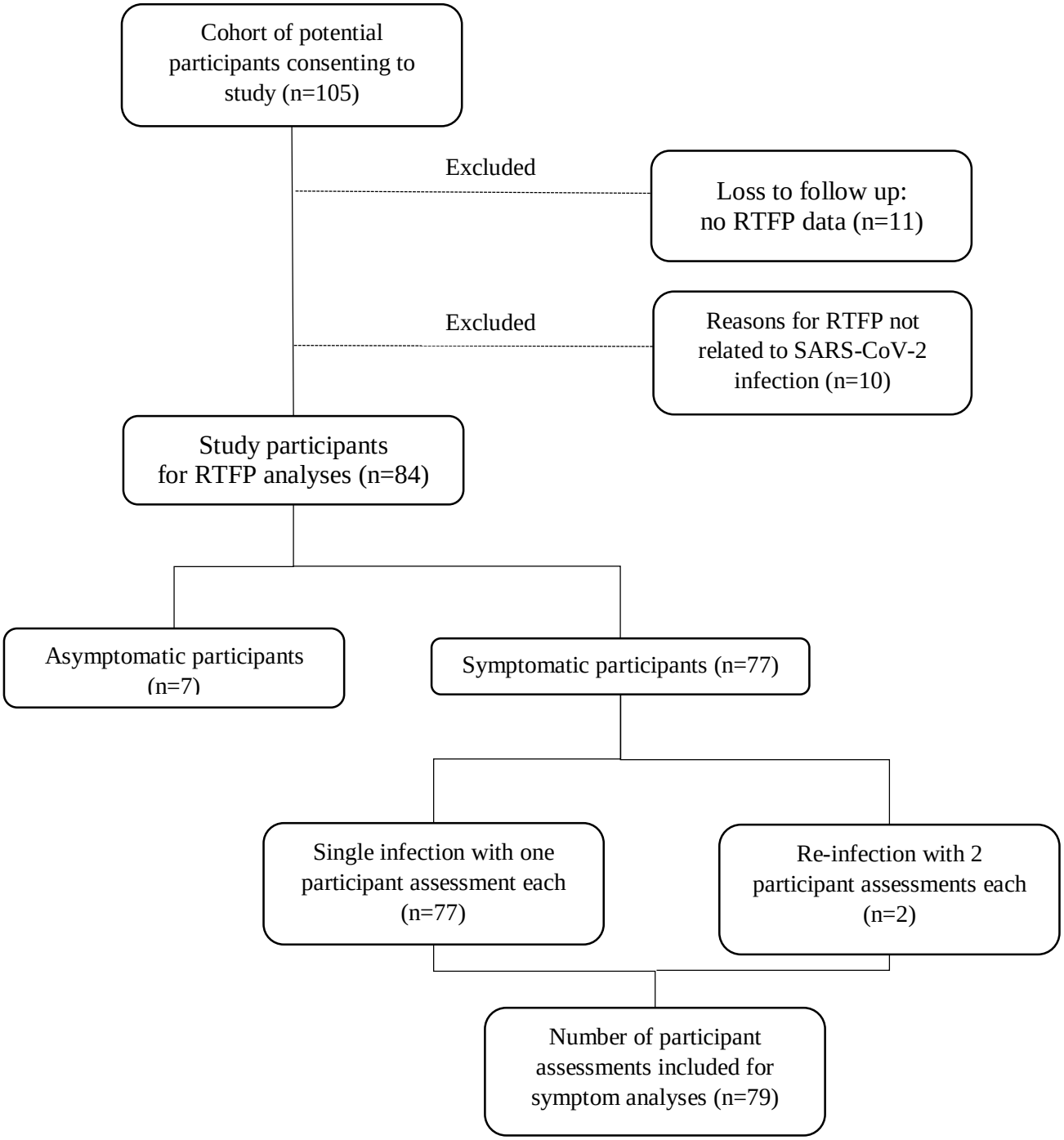
Anatomical region	Symptom	n	Hazard Ratio (95%CI) #	Chi-Square	p-value
Nose and Throat	**Any Nose and Throat**	**79**	^	^	^
	Sore/scratchy throat	47	0.73 (0.45-1.18)	1.67	0.196
	Hoarseness	13	0.83 (0.52-1.33)	0.61	0.434
	Blocked/plugged nose	52	0.70 (0.43-1.13)	2.19	0.139
	Runny nose	21	0.70 (0.43-1.14)	2.07	0.150
	Sinus pressure	39	0.93 (0.59-1.46)	0.100	0.752
	Sneezing	10	-	-	-
	Altered/loss sense of smell	45	0.63 (0.38-1.02)	3.57	0.059
	Altered/loss sense of taste	40	0.64 (0.41-1.02)	3.50	0.061
Chest and Neck	**Any Chest and Neck**	**68**	0.35 (0.19-0.63)	11.95	**0.0005**
	Dry cough	28	0.76 (0.47-1.21)	1.35	0.246
	Wet cough	33	0.82 (0.52-1.29)	0.72	0.395
	Difficulty in breathing	18	0.70 (0.46-1.07)	2.68	0.102
	Fast breathing/shortness of breath	18	0.65 (0.42-1.0)	3.78	0.052
	Chest pain/pressure	21	0.53 (0.33-0.84)	7.44	**0.006**
	Chest tightness	14	0.56 (0.31-0.95)	4.60	**0.032**
	Headache	47	0.54 (0.34-0.87)	6.62	**0.010**
	Red/watery/scratchy eyes	14	0.68 (0.43-1.06)	2.93	0.087
Whole Body	**Any Whole Body**	**63**	0.40 (0.21-0.75)	8.18	**0.004**
	Fever	26	0.55 (0.35-0.88)	6.14	**0.013**
	Chills	24	0.55 (0.34-0.90)	5.67	**0.017**
	Excessive fatigue	49	0.32 (0.19-0.53)	20.00	**<.0001**
	General muscle aches and pains	41	0.57 (0.37-0.89)	6.11	**0.014**
	Skin rash	1	-	-	-
	Abdominal pain	8	-	-	-
	Nausea	11	0.54 (0.31-0.94)	4.73	**0.030**
	Vomiting	1	-	-	-
	Diarrhoea	6	-	-	-
	Loss of appetite	22	0.49 (0.30-0.81)	7.63	**0.006**

HR is the ratio of the hazard of RTFP for an individual with the symptom compared to the hazard of RTFP for an individual without the symptom. A HR<1 indicates a higher chance for prolonged RTFP after the onset of infection for an individual with the symptom compared to an individual without the symptom

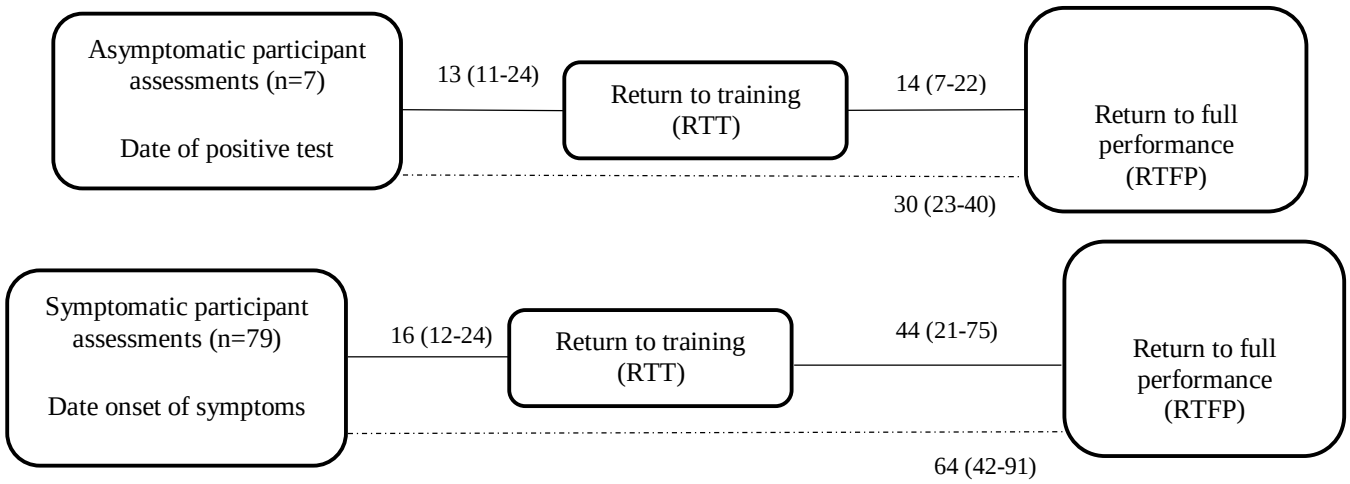
^ All participants had at least one "nose and throat" symptom

- Numbers too few to calculate HR

Supplementary figure 1: Study participants and number of participant assessments



Supplementary figure 2: Duration days from onset of symptoms or positive test to RTT and RTFP



THE END