



**Medical Consequences in Endurance Sports-
Two Oceans Marathon longitudinal study:**

**An evaluation of participation guidelines in
runners presenting with symptoms of acute illness
before competition**

**A dissertation prepared by Leigh Gordon (*DNLLEI001*) in
partial fulfilment of the requirements for the Master of
Philosophy degree in Sport and Exercise Medicine (MPhil
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List of abbreviations

ACSM	American College of Sport Medicine
ADH	Anti-diuretic hormone
AQUA	Allergy Questionnaire for Athletes
ARF	Acute renal failure
ASOT	Anti-streptolysin O titre
BASES	British Association of Sport and Exercise Science
CBC	Complete blood count
CDC	Centre for Disease Control and Prevention
CK-MB	Myoglobin binding fraction of creatine kinase
CMV	Cytomegalovirus
CON	Control
COPD	Chronic obstructive pulmonary disease
CRP	C Reactive Protein
DNF	Did not finish
DNS	Did not start
EBM	Evidence-based medicine
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EHS	Exertional heatstroke
EIB	Exercise-induced bronchospasm
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
FEV ₁	Forced expiratory volume in 1 second
FINA	Federation Internationale de Natation
GABHS	Group A β -Haemolytic Streptococcus
HIV	Human immunodeficiency virus
HR	Heart rate
HRR	Heart rate reserve
IAAF	International Association of Athletics Federations
IgA/M/G/E	Immunoglobulin A/M/G/E
Il-6	Interleukin 6
IM	Infectious mononucleosis

IP	Incidence Proportion
IR	Incidence Rate
ISEI	International Society of Exercise and Immunology
LRTS/I	Lower respiratory tract symptoms /infection
MC	Medical complication
NK	Natural Killer
NSAIDs	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PCT	Pro-calcitonin
PRIMA	Pre-Race acute Infection Medical Assessment
PRIMA-I	Pre-Race acute Infection Medical Assessment – Infection
PRIMA-N/I	Pre-Race acute Infection Medical Assessment – Non-Infection
RSV	Respiratory Syncytial Virus
RTP	Return- to-play
SCD	Sudden cardiac death
SEM	Sport and Exercise Medicine
SIRS	Systemic inflammatory response syndrome
UK	United Kingdom
URT	Upper respiratory tract
URTI	Upper respiratory tract infections
URTS	Upper respiratory tract symptoms
WARI	Wheezing after Respiratory Tract Infection
WCC	White cell count

Abstract

Background:

One of the most common clinical decisions a Sports and Exercise Medicine (SEM) physician is required to make is whether an athlete presenting with symptoms or signs of an acute illness can participate in exercise training or competition. Currently, a clinical tool, known as the ‘neck check’ is used to determine eligibility to participate in exercise training or competition athletes with acute illness. This original clinical tool, first described about 20 years ago, was based mainly on an abbreviated medical history and findings of a clinical examination were excluded. Symptoms of illness ‘above-the-neck’ *e.g.* sneezing, rhinorrhoea or sinus congestion constitute a ‘passed’ “neck check”, whereas ‘below-the-neck’ symptoms *e.g.* cough and/or systemic symptoms such as fever and myalgia, constitute a ‘failed’ “neck check”. However, in the current literature, there remain very few data regarding 1) the adherence of athletes to advice given following a ‘neck check’, and 2) whether the exercise performance (*e.g.* the ability to finish a race) or the development of medical complications during exercise is different in athletes who “passed” or “failed” the ‘neck check’.

Objective

The main objectives of this dissertation are: 1) to review the available evidence with respect to medical assessment and participation risk in endurance runners presenting with symptoms of acute illness before a road race; 2) to document the range of acute illnesses in runners presenting in the 3 days before a race; 3) to determine adherence to advice given by medical staff to these runners, and 4) to determine the effects of the outcomes of the medical assessment on running performance particularly, the ability to finish the race and the medical complications experienced during the race. These data are important to improve the medical care of runners (and other athletes) presenting with acute illness before training and competition.

Methods

Phase 1: Review of the literature

All literature relating to the epidemiology of acute illness in athletes, risk factors for illness, and participation risk, potential medical complications and effects on performance of exercising whilst ill were sourced using established electronic databases (PubMed, Medline, Google Scholar). In addition, literature related to the background of the ‘neck check’, as well as the evolution of the current RTP guidelines in athletes with acute illness were sourced.

Phase 2: Research study

In a prospective cohort study, 242 runners who presented to a pre-race registration medical facility with medical concerns were assessed by SEM physicians by means of medical history and physical examination (if indicated) using a specific **P**re-**R**ace acute **I**llness **M**edical **A**ssessment (PRIMA group). 172 of these runners had evidence suggesting acute infective illness (PRIMA-I group) and 70 runners had non-infective complaints (PRIMA-N/I group). The epidemiology (prevalence rate = % runners) of runners with symptoms, signs and specific clinical diagnoses of acute illnesses were documented in the PRIMA-I group. Following clinical evaluation, all the runners in the PRIMA-I group were then advised regarding clearance to run the race, monitoring symptoms, or not running the race, using the ‘neck check’ as a guideline. Runners in the PRIMA cohort were then tracked during and immediately after the race, and the following parameters were compared to those in a control group of runners not presenting to the medical facility at registration (CON=53 734): 1) incidence of not starting of the race (per 1000 runners) (DNS rate), 2) incidence of not finishing the race in those who started (per 1000 runners) (DNF rate), and 3) incidence of medical complications during the race in those who started (per 1000 runners) (MC rate).

Results

Phase 1: Review

The main finding of the review is the relative paucity in clinical data with respect to participation in athletes with acute illness. Upper respiratory tract symptoms are very common in athletes, and the risk factors are discussed. Furthermore, there are different aetiologies underlying athletes’ URT symptoms (other than infection). The documented risks of exercising when systemically ill include sudden cardiac death and reduced pulmonary function, splenic rupture in patients with infectious mononucleosis, and dehydration and electrolyte disturbances when exercising with acute gastro-intestinal illness. There is little evidence in the literature regarding the effects of illness on performance; these include reduced performance, non-participation and the potential effects of WARI (wheezing after respiratory tract infection). Evidence supporting the two aspects of the neck check is reviewed: the presumed safety of exercising with localised URT symptoms, and the perceived risk of exercising with lower respiratory tract or systemic symptoms. Clinical data are severely lacking, and the available data are based on self-reported symptomatology. There are no published data regarding the use of the ‘neck check’ as a participation guideline.

Phase 2:

In the PRIMA-I cohort of 172 runners, the most common symptoms were sinus congestion (40.1%), cough (38.2%), sore throat (37.8%) and runny nose (25.6%). More than half the cohort (57.5%) had a diagnosis of localised URTI. However, URTI with generalised symptoms was the single most common diagnosis (22.7%). In the PRIMA-I group, 41.3% of the runners failed the 'neck check'. Compared with the CON group, there was no significant difference in the DNS rate in the PRIMA-I group. However, in those runners who were advised not to run, the DNS rate was 565 per 1000 runners, and this was significantly higher than that of the CON group (192 per 1000 runners) ($p < 0.0001$). PRIMA-I race starters had a higher DNF rate (31 per 1000 runners), and runners with any medical concerns (PRIMA group) had a significantly higher DNF rate (37 per 1000 runners) compared to the CON group of runners who started the race (15 per 1000 runners) ($p = 0.0329$). There were no documented medical complications in the PRIMA-I group who started the race, while the MC rate of the CON group was 6.7 per 1000 runners. In runners in the PRIMA-I group who had been advised not to run, 43.5% were non-adherent, and started the race despite this advice.

Conclusion

Our study indicates that localised upper respiratory tract infection is responsible for the majority of acute illness in a pre-race cohort of runners. Furthermore, the data provide some evidence that it is safe for runners with acute illness to exercise if they pass the 'neck check'. However, presenting to a pre-race registration medical facility, failing the 'neck check' and receiving advice against participation appear to increase the risk of not finishing a race. There is also concern about the high rate of non-adherence to advice given by the SEM physician. Finally, a pre-race registration medical assessment for runners with acute illness may reduce the risk of developing short-term medical complications during the race.

Key words: illness, exercise, neck check, participation guidelines, return-to-play, adherence

Chapter 1

Introduction and scope of the thesis

One of the most challenging clinical decisions a Sport and Exercise Medicine (SEM) physician is required to make is: “When can an athlete with symptoms of a recent or current acute illness train or compete?” In this context, most acute illnesses refer to infective illness, and this will be the focus of this dissertation. Where appropriate, other non-infective acute illness will be specifically highlighted.

This apparently simple question conceals a myriad of complex clinical, health and safety, performance, and even medico-legal issues, all of which the SEM physician needs to consider. Some of the pertinent questions are:

- Are athletes at particular higher risk for becoming acutely ill (with infective illness), and if so, why?
- When, if ever, is it safe to exercise whilst sick, or does it depend on the type of acute infective illness?
- What are the theoretical and documented risks of exercising whilst acutely ill with an infection? When is it safe to return to play after acute infective illness?
- What are the guidelines for the athlete, and do they adhere to the advice given by the SEM physician?

Modern day evidence-based medicine (EBM) requires SEM physicians to keep abreast of the latest evidence and guidelines regarding management strategies, as for all other specialities. Therefore, a fundamental question for the SEM physician is whether there are any EBM guidelines to address the above-mentioned questions.

In this dissertation, the first aim will be to review the existing literature, and to explore the current evidence to answer the above-mentioned questions (Chapter 2). More specifically, in Chapter 2 the available literature regarding acute illness and exercise, with a focus on what is relevant to participation guidelines, will be reviewed. The first section in this Chapter will explore the assessment of the acutely ill athlete from multiple perspectives, including the epidemiology and risk factors of symptoms of infection.

The second half of Chapter 2 aims to explore available return-to-play (RTP) guidelines following acute infections. Safe RTP advice requires a solid evidence base on which to build safe RTP guidelines. It is this evidence base which will be under scrutiny.

In Chapter 3, the details of an original research study will be presented. The aim of this prospective cohort study in 172 runners was to determine if runners who presented to a pre-race registration medical facility with acute illness, and then clinically evaluated and advised regarding exercise participation: 1) adhered to advice (starting the race or not); 2) finished the race (in those who did start the race); and 3) required treatment at the race medical facilities (medical complications) (in those who started the race). These data will make a significant contribution towards the evidence base in this field of Sports and Exercise Medicine. To our knowledge, this is the first study that examines the application of the principles of the 'neck check' as the basis for RTP decisions, particularly evaluating athletes who exercise with symptoms of localised illness. Furthermore, it is also the first time that the concept of athletes' adherence to RTP advice has been explored.

Finally, in Chapter 4, the results from this dissertation will be summarised. Clinical guidelines for SEM physicians will be provided, and directions for future research will be explored.

Chapter 2

A review of participation guidelines for athletes presenting with symptoms of acute illness

2.1. Introduction

Traditionally, the role of the Sport and Exercise Medicine (SEM) physician has been pivotal in the assessment, diagnosis and management of sports injuries, together with the management of chronic medical conditions in athletes, both recreational and elite. Over the past two decades the literature indicates an increasing interest in diagnosis and management of acute illness in athletes.

Infections are common in athletes, and SEM physicians are required to accurately identify symptoms of infection and manage athletes appropriately. For the athlete, the most important question is usually: “When can I exercise again?” There are many factors that may influence the physician’s decision: some are medical, but others include external factors such as pressure from family, coaches and other players. Creighton *et al* described a 3-step decision-based model for return-to-play (RTP) after illness or injury, although their model mostly discusses injury (1).

The first step is the ‘Health Assessment’ of the athlete, considering the relevant medical factors, including history, examination and special investigations. The second step is ‘Participation risk’, considering athlete-specific factors *e.g.* their type of sport, and in the context of illness, the required aerobic capacity. This step requires knowledge of the potential complications of exercising with the acute illness. The third and final step considers ‘Decision modifiers’, which introduce external factors such as the type and level of competition and pressure from coaches *etc.* These modifiers may alter the participation risk for an athlete’s health status at a given time. It should be noted that the acceptable risk threshold for each individual might differ (1). Creighton’s model will provide the basic structure for the first part of this literature review.

‘Health assessment’ is the first step in the decision-making process when faced with an athlete who has symptoms of acute illness, and will thus be the first area to be reviewed. The SEM physician should be cognizant of the multi-faceted nature of the assessment. The epidemiology of acute illness in athletes in the pre-competition period will also be briefly discussed, as well as the

risk factors for developing acute illness during this time. It has been proposed that some acute upper respiratory tract symptoms, presumed to be infectious in origin, may in fact have a different aetiology, and the evidence for this will be reviewed.

The second part of the 'Health Assessment' will focus on the medical factors that comprise the clinical evaluation of the athlete. Most of the evidence in the literature consists of epidemiological studies where athletes have self-reported symptoms of infection during periods of training or after competition. An accurate health assessment requires a sound clinical diagnosis based on a medical history and a physical examination. In this section of the review the role of clinical evaluation in athletes with symptoms of illness will be explored. An accurate diagnosis, especially depending on whether the aetiology is infective or other, is key to effective management and consequently, safe RTP advice.

The second step in Creighton's model is 'Participation Risk'. Although Creighton's discussion is focused on injury, the concept is equally pertinent in illness. This section of the review will therefore discuss the evidence regarding potential medical complications of exercising whilst suffering from an acute illness, as well as the potential effects on exercise performance. Understanding the participation risks when ill is an essential element of providing safe RTP advice. However, there is a paucity of literature on this topic, and data are mostly from epidemiological studies, or from a limited number of animal studies. Part of the reason for the paucity in data is that it would be unethical to perform randomized studies in acutely ill athletes.

The potential risks of exercising when ill are often difficult to quantify, and each athlete may have an individual threshold of "acceptable risk". Furthermore, this threshold may change depending on the third step of Creighton's model – 'Decision modifiers'. This last step will only be mentioned briefly in the review. Decisions therefore need to be discussed with the athlete, and other role players such as the coach to ensure that informed decisions are made. However, it is most important that the SEM physician takes the final RTP decision (2, 3).

The second part of the literature review will explore the evidence base for current RTP guidelines in athletes with acute illness. RTP guidelines need to consider all of the issues discussed in the first half of this chapter. Ideally, these guidelines should be evidence-based, as required of other guidelines in the medical field *e.g.* the rigorous data, both clinical and economic, required for the NICE (National Institute for Health and Care Excellence) guidelines in the UK. The evidence that

is required for the development of a RTP guideline should be specific for the illness, and may be modified by the athlete's sport. Besides the issues that will be discussed under Creighton's model, other considerations include:

- Is there a difference in risk between localised *vs.* systemic infection?
- Is there a difference in risk, which is related to the primary site of the infection?
- Is the risk associated with the specific infective organism, or the symptoms?
- If there is evidence of harm, is it due to the infective organism, or associated systemic symptoms if they are present?
- Is there a risk of transmission of the illness to other athletes?

It should also be noted that both the SEM physician, as well as the athlete, need to be in agreement about their definition of RTP *e.g.* anywhere on the spectrum from partial training at low exercise intensity to full competition without any restriction. Once a guideline has been developed, it is ideal to have evidence of clinical impact, and this will be discussed with the Bethesda guidelines for RTP after myocarditis.

Current RTP guidelines for athletes following acute illness are based on a clinical tool known as the 'neck check'. Therefore, the evidence base for this guideline and the evolution thereof will be discussed. For the remainder of this dissertation, this clinical tool and guideline will be referred to as the neck check. Currently, evidence-based RTP guidelines only exist for two defined infective conditions: myocarditis and infectious mononucleosis (IM) (3-8).

2.2. 'Health Assessment' of the athlete with symptoms of acute illness

In this section the epidemiology of upper respiratory tract symptoms (URTS) in athletes, as well as the risk factors for symptoms of upper respiratory tract infection (URTI) will first be reviewed. Thereafter, the role of the 'health assessment', specifically the clinical evaluation in an athlete with symptoms of acute illness, will be reviewed.

2.2.1. Epidemiology of acute illness in athletes in the pre-competition period

2.2.1.1. Introduction

In the past 2-3 decades, the majority of the literature relating symptoms of acute infective illness to exercise participation has been from the field of exercise immunology. This field has largely focused on the measurements of immunological responses to acute exercise bouts or regular exercise training, mostly in healthy participants. In very few studies, have any acutely ill athletes been studied, or have clinical measurements and outcomes been determined. Although there have been some excellent reviews of the known changes in the immune system following an acute bout of strenuous exercise (9, 10), there are very limited applications of these data to the clinician faced with RTP guidelines for an acutely ill athlete. Therefore, it is outside the scope of this Chapter to perform a detailed review of the immunological response to acute and chronic exercise by the immune system. However, some of the relevant aspects will be briefly reviewed. It is very important to note that, to date, no causative relationship has been established between exercise-related immunological changes and the apparent increased risk of URTI in athletes, or the increase in post-race URTS (9, 11).

Furthermore, there are almost no data regarding the epidemiology of acute illness in athletes in the pre-competition period. As previously mentioned, most of the clinical data in exercise immunology have been based on self-reported symptomatology by athletes. More recently, data have been reported regarding illness patterns in different groups of athletes from different sporting codes and ability levels (elite vs. recreational).

For a long time, it was presumed that the upper respiratory tract symptoms seen in athletes post-competition were infectious in nature (hence URT Infection - URTI). However, a growing body of evidence suggests that upper respiratory tract (URT) symptoms are also common in the pre-competition period and may have a non-infective aetiology; thus they should rather be referred to as URT symptoms (URTS) (12-18).

These non-infective URT symptoms may also be responsible for many of the symptoms which appear to comprise the athlete's general 'increased risk of infection' (12, 17), thereby correlating

with pre-race URTS. There appears to be a strong link between pre- and post- race symptoms, suggesting a common aetiology and some of these data can be summarized as follows:

- A study of 70 elite level athletes seen in a SEM clinic, reported a clinical diagnosis of viral / bacterial URTI in 87%. Infectious pathogens were only isolated in 57% (12).
- A study of 104 ultra-distance marathon runners investigated post-race URTS. 35 runners developed URTS after the race, but there was no significant difference in pre- and post-race blood results (CRP, CBC, Serum IgA or ASOT). Viral and bacterial cultures failed to isolate anything other than scanty numbers of normal commensals (13).
- Immunoglobulin levels were measured in 14 randomly selected Comrades (ultra-marathon) runners from 4 weeks before until 2 weeks after the race. The incidence of URTI was highest 4 weeks prior and 7-14 days after the race. URTI symptoms were not associated with a change in secretory immunoglobulin levels, and there appeared to be a strong correlation between pre-race and post-race symptoms, suggesting re-activation of the underlying aetiology (19).
- A strong correlation was shown between pre- and post-race self-reported symptoms in 1694 Stockholm marathon runners (15).
- A study investigating the prevalence of allergy in runners of the London Marathon showed that 40% of the runners were 'allergic' before the race, as defined by a positive AQUA questionnaire and confirmatory raised total / specific IgE. Many allergic symptoms *e.g.* rhinitis, would be classified as URTS in a symptom questionnaire (17).
- A prospective study of 32 elite triathletes, 31 recreational triathletes and 20 sedentary controls was carried out over a 5-month period, which spanned competition and training. An increase in URTS was found in the elite and control athletes, but a pathogen (mainly rhinovirus) was only isolated in less than 30% of these runners. Microscopy, culture, PCR and serology tests were all performed (16).
- The use of topical "fusafungine" spray has been shown to reduce the incidence of post-race URTS by 23% in ultra-marathon runners. Viral and bacterial cultures were negative, suggesting that the aetiology was inflammatory rather than infective (18).

These data are suggestive that not all URTS in athletes are infectious in origin, and that the SEM physician should consider other causes of URT inflammation, including allergies, as the cause of URT symptoms. If these symptoms (of as yet unknown aetiology) are present during general training and pre-race periods, it is quite feasible that the same aetiology is associated with the post-race symptoms.

2.2.1.2. Epidemiology of URTI in the pre-competition period

There are very few clinical data regarding the prevalence of acute illness in the pre-competition period. As discussed earlier, most of the data relate to self-reported symptoms only, and mostly on post-race URTS. Recent studies have reported the incidence of illness in tournament settings, where it has consistently been shown that respiratory symptoms are the most common, followed by gastro-enterological and dermatological symptoms respectively (20-25). A study of the incidence rate of acute illness in Paralympic athletes showed no difference between the 3 days pre-competition as compared to during the Games period (20). For many of these athletes, the timing of their illness would have corresponded with their pre-competition periods. Neither this study, nor those mentioned above, differentiated whether the athletes' illness was pre- or post-event.

2.2.2. Risk factors for acute illness in the pre-competition period

The identification of risk factors of acute illness in athletes allows the SEM physician to address known modifiable risk factors so that preventative programs can be planned and implemented. In cases where non-infective aetiology may be implicated, the ability to recognise these factors may help direct appropriate management. Risk factors that may be associated with increased risk of illness (mainly URTS) will now be reviewed.

2.2.2.1. Increased training load causing increased URTS

Over 20 years ago, it was suggested that the risk of developing URTS is related to the training load of the athlete (26). This relationship was described as a 'J curve' and was based on an analysis of a mixed cross-sectional cohort of marathon runners and sedentary people, as well as longitudinal studies in athletes and sedentary men and women (27). According to this hypothesis, moderate exercise activity reduces the risk of developing URTS compared to sedentary people, whilst strenuous and/or prolonged exercise increases the risk of URTS (more so than for sedentary people) (Fig. 2.2.2.1.)(26). Evidence in support of this hypothesis was a documented increased incidence of URTS in elite triathletes compared with control subjects (16). Similar observations were reported in other studies to support this hypothesis (27).

However, an S-curve has also been described to define the relationship between training load and the development of URTS. This was described following a re-evaluation of published data, and adapting the J curve to distinguish between ‘high load’ and ‘elite’ athletes, where the elite athletes were shown to have a lower risk for infection (Fig. 2.2.2.2) (27). These relationships between training load and risk of URTS will have a direct impact on the risk of pre-competition illness, which is the focus of this dissertation.

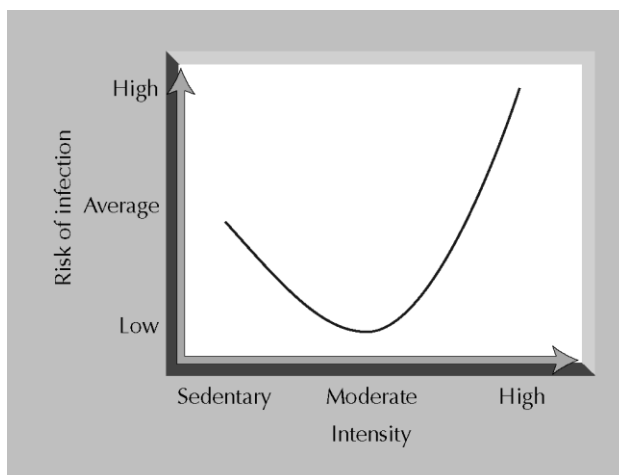


Fig. 2.2.2.1: The relationship between training load and risk of URTS (‘J shaped’ curve) (26)

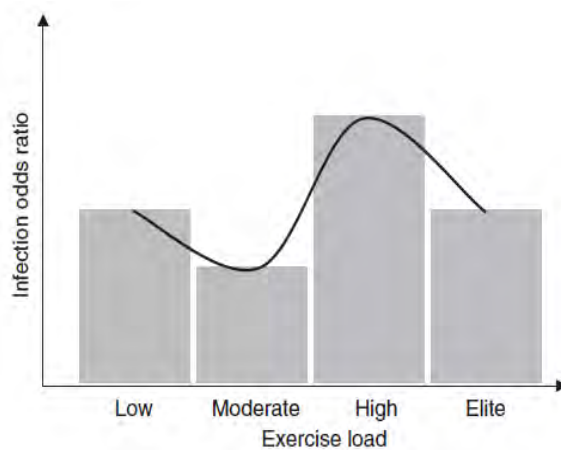


Fig. 2.2.2.2: The relationship between training load and risk of URTS (‘S shaped’ curve) (27)

A review in 1993 examined the relationship between training load and URTS risk (28). However, the studies discussed in this review mainly focused on increased training mileage and the physiological stress of racing with respect to post-race URTS (29, 30). It has been shown that

training volumes of >97 km/week were associated with increased URTS during training periods, which would coincide with pre-race risk (30).

However, not all studies are in accordance with these findings – a large study compared the point prevalence of self-reported illness 3 weeks before and after the Stockholm marathon. In this study, the pre-race prevalence of self-reported illness was 17% and the post-race incidence was 19%. However, in those athletes without pre-race illness, the incidence of post-race illness was only 16%, thereby not supporting the hypothesis that URTS are increased after exhaustive exercise. Therefore the results of this study did not support the correlation between pre-race training volume (load) and increased post-race symptoms, but it did support the hypothesis that pre-race symptoms increase the risk of post-race symptoms (15).

2.2.2.2. Gender

Several studies have reported a significantly higher incidence of illness in female athletes participating in tournament settings (23, 24, 31). In one study, the incidence of illness was more than double in female athletes participating in the Youth Olympic Games (22). However, in another study during the 2012 Paralympic Games there was no association between gender and overall risk of illness (20).

2.2.2.3. Age

In some studies it has been documented that older age is associated with an increased risk of illness in athletes participating in tournaments. Older women were noted to have increased illness in the Winter Olympics (24) and older age was associated with increased illness in the IAAF tournament (31). However, this was not confirmed during the 2012 Paralympic Games where there was no association between older age and overall risk of illness (20).

2.2.2.4. Travel

Recently, it has been shown that the incidence of acute illness in elite athletes increases by 2-3 fold when travelling across more than 5-hour time zones to a distant country (32). This increased incidence returned to baseline on the athletes' return to their home country. This implied that the underlying reasons were factors related to the distant destination, as opposed to travel *per se*.

Travel allows for teammates to be in closer proximity for longer periods of time, increasing the risk of transmission of viral infection (33). Travel in general may also expose athletes to food-borne illness, causing acute gastro-intestinal infection (34). These factors may certainly influence the risk of pre-competition illness.

2.2.2.5. Allergy

A pre-race screen of 208 runners at the 2010 London Marathon reported that 40% of runners had allergies, as defined by a positive AQUA questionnaire and a raised total or specific IgE. Runners with a history of infection in the 2 weeks pre-race were excluded from this study. The post-race incidence of URTS was 47%, and a history of allergy was a significant risk factor for URTS. The controls in this study were non-runners from the same household, and only 19% had symptoms, suggesting that many of the symptoms were not infectious in origin (17). Therefore, symptoms of allergy may mimic those of infection in the pre-competition period.

2.2.2.6. Environment

It has been documented that a significant increase in respiratory symptoms is seen in winter endurance sports such as Nordic skiing and skating (24, 35). Bronchial hyper-reactivity has been noted in many of these winter endurance athletes, and it is postulated that a combination of factors may be responsible for this including: cooling and drying effect of breathing cold air, hyperpnoea-related epithelial injury, and inhalation of noxious gases in the case of indoor skating (35, 36). Training in such an environment would increase the risk of pre-competition respiratory tract symptoms in these sports. A clinical assessment would be particularly important to differentiate between inflammatory symptoms, and those presumed to be infectious in origin.

2.2.2.7. Type of sport

In recent years, a number of studies reported differences in the incidence of illness in different sporting codes. More specifically, it has been shown that there was a higher incidence rate (IR) of illness in track and field athletes, compared with other sporting codes, during the 2012 Paralympic Games (20). Similarly, data from swimmers participating in the FINA World championship showed that there was a significant difference in illness rates between the different aquatic disciplines (23).

2.2.2.8. Other factors

Individual susceptibility to infection may be influenced by an athlete's immuno-competence, their response to exercise stress and recovery, exercise capacity and non-training stressors (10). Other factors that increase an individual's vulnerability to infection have been described, but these have not been well investigated in athletes. These factors include 1) nutritional deficiencies (*incl.* micronutrients), 2) sleep disruption (reduced quantity and quality, as well as chronic sleep deprivation) and 3) chronic psychological stress (10).

2.2.2.9. Summary: Factors related to increased risk of illness

In summary, risk factors that may increase the risk of symptoms of illness in the pre-competition period include: increased training volume, travel (especially across >5 time zones to a foreign destination), allergy, exercise environment, and type of sport. Female gender and increased age may also be risk factors, but this requires further investigation.

2.2.3. The role of a pre-race medical assessment in the athlete with symptoms of acute illness in the pre-competition period

A medical assessment, consisting of at least a medical history and a physical examination is the first step for any SEM physician when evaluating an athlete who presents with symptoms of an acute illness before a competition or a training session. Following this assessment, a sound clinical diagnosis can be made or further investigations may be performed. This can then be followed by advice on RTP. Anecdotally, there is evidence that RTP advice is often frequently given on the basis of symptoms only (medical history). However, as indicated in the previous section, upper respiratory tract symptoms may have different aetiologies, and therefore a physical examination is not only important to distinguish a non-infective from an infective cause of URTS, but also to distinguish localised from systemic symptomatology. These factors may influence the decision to compete, and also the risk of reduced exercise performance or medical complications. However, to our knowledge, this has not been studied in the context of RTP guidelines for acute illness in athletes.

This section will review aspects of the clinical evaluation that would facilitate the assessment of the athlete with symptoms of acute illness. The medical history will be discussed first, with the

focus on the importance of clinical interpretation of constellations of symptoms. The following section will describe typical examination findings that suggest infection. Finally, the use of special investigations will be addressed, where these may be valuable in 1) differentiating infective from non-infective causes, and 2) obtaining a definitive diagnosis in the assessment of the athlete with symptoms of an acute illness before a competition.

2.2.3.1. Medical history

The value of a clinician interpreting an athlete's symptoms is significant. Many athletes presume their symptoms are infective in origin, but this may not always be the case (as previously discussed). The SEM physician is in a position to identify other aetiologies such as allergies. Common URTS such as rhinorrhoea (runny nose), sore eyes and pharyngeal discomfort may all be present in either an URTI, or be allergy-related. For a clear definition of an URTI, some authors have used a validated symptom checklist and recommended that an URTI required ≥ 3 symptoms from this checklist (37). It has been established that allergies may be more prevalent in endurance athletes (17). Furthermore, URTS are more common in winter endurance athletes (35), where URT symptoms may also be related to high volumes of cold dry air causing mucosal injury, rather than infection.

2.2.3.2. Physical examination findings

As far as we are aware, there are no published data on the specific value of findings on clinical examination in the RTP guidelines given to athletes presenting with an acute illness in the pre-competition period. Current RTP guidelines after acute illness (the neck check) are based on self-reported symptoms only. By inference, there is no mention in the literature of the indications for physical examination in athletes with symptoms of acute illness in the pre-competition period. When examining an athlete with symptoms of acute illness, one of the aims of the medical assessment is to differentiate infective from non-infective symptoms. However, it has been shown that clinicians may not always consider non-infective symptoms as a differential diagnosis for URTS (12). In this study, clinicians diagnosed 30% of athletes as having an infection for which there was no laboratory evidence.

In order to diagnose a systemic inflammatory response syndrome (SIRS), two of the following four criteria are required for diagnosis (38):

1. Raised body temperature

There are normative values for different sites of temperature measurement. Circadian rhythm should be borne in mind. With a move away from mercury glass thermometers, infra-red aural thermometers are now commonly used. A systematic review of the accuracy of peripheral aural (and oral) thermometry indicates that these methods give an accurate representation of core temperatures within the febrile range and can thus be recommended for this purpose (39).

2. Raised resting heart rate (>90 beats / min)

It is well established that a fever is associated with a tachycardia, as compensation for reduced stroke volume (SV) (8). Additionally, a difference of 10-20 beats / min in resting HR on waking in the morning may indicate the onset of illness or represent inadequate recovery (40, 41). This requires close monitoring of the athlete on a daily basis, and without this prior knowledge of the athlete's normal values, it is limited as a criterion for decision-making in the clinical setting. In addition, athletes have a training-induced reduction in resting heart rate, and to use resting heart rate cut-offs from the general population is not appropriate.

3. Increased respiratory rate (>20 breaths/min)

It is well established that there might be tachypnoea in an acute systemic infective condition. This may be as a result of hyperventilation related to temperature regulation or hypoxia.

4. Full blood count (FBC) - mainly white cell count (WCC)

An abnormal WCC ($>12 \times 10^9/L$ or $<4 \times 10^9/L$, or $>10\%$ immature forms) is the fourth criteria that can be used to diagnose a SIRS.

In most instances, team physicians and SEM physicians advising athletes with acute illness may not have the FBC results available in time to make the RTP decision. Therefore, as objective signs of a systemic illness, SEM physicians often have to rely on clinical signs (raised body temperature, increased resting heart rate and resting respiratory rate) to diagnose a SIRS.

Furthermore, to determine the source of the infection, it is often difficult to differentiate between bacterial and viral causes of certain URT conditions such as sinusitis and pharyngitis. Both the medical history and a physical examination have a poor sensitivity and specificity for distinguishing between viral and bacterial causes (33). However, the Berg prediction rule has been used to help identify bacterial infection. According to this rule, the presence of focal sinus tenderness and purulent nasal discharge increase the risk of the causative organism being bacterial in nature (42). Allergy may produce sinus congestion as well, but in this case the nasal

discharge should be clear and no systemic symptoms (such as fever, myalgia or arthralgia) should be present. Lower respiratory tract symptoms such as a cough may be present as a result of a post nasal drip or concurrent asthma. Other symptoms such as sneezing and particularly itchy eyes may indicate the presence of allergy. Sinus aspiration culture is the gold standard for diagnosis of bacterial sinusitis, but is rarely used in a clinical setting.

A sore throat may be a symptom of many clinical conditions including simple viral URTI, bacterial pharyngitis, or infectious mononucleosis (IM). It may also be associated with a post-nasal drip or mouth breathing at night. Examination is thus indicated to identify the possibility of bacterial pharyngitis (usually due to *Group A β -Haemolytic Streptococcal infection – GABHS*), which is often difficult to distinguish from IM. Posterior cervical lymphadenopathy and additional signs such as splenomegaly or hepatosplenomegaly may be indicative of IM (42).

As mentioned earlier, there is evidence that that laboratory-based classification provided better differentiation of infection than clinical diagnosis based on symptoms and signs. Predictors for partially distinguishing infective episodes included: presence of a high number of systemic symptoms, elevated WCC and neutrophilia, self-imposed training modifications and lower Vitamin D concentrations (12).

2.2.3.3. Special investigations

The following discussion looks at three of the questions SEM physicians should be asking themselves when they see an athlete with symptom of acute illness, as the answers will obviously impact on their management, and consequently the RTP advice given:

- a) Is this illness a result of an infective process? If so, can a viral infection be differentiated from a bacterial infection?
- b) Is there evidence of specific conditions such as pharyngitis, where different aetiologies will have different RTP guidelines *e.g.* GABHS and IM?
- c) Can myocarditis be excluded?

a) Is this an infective illness? Bacterial vs. viral?

Traditionally, inflammatory markers such as ESR and CRP have been done, together with a WCC + differential count. However, ESR, CRP and lactate have poor sensitivity and specificity for infection (38, 43). These are elevated in systemic inflammation, whatever the cause, be it auto-

immune, surgical stress, burn stress or infection. A neutrophilia is the common response to bacterial infection, while a neutropaenia may be seen in viral infections.

Novel biomarkers target bacterial sepsis, due to its high morbidity and mortality. **Pro-calcitonin (PCT)** is a strong indicator of bacterial infection (43). Although several new biomarkers have been identified for sepsis, none has ideal individual sensitivities or specificities. Examples of such biomarkers include **IL-6** (Interleukin-6), **LBP** (lipopolysaccharide-binding protein), **CD64 counts and TREM-1** (triggering receptor expressed on myeloid cell 1) (43-45). None of these are appropriate / practical for the classical SEM consultation, where a simple biomarker of infection would be helpful.

Vitamin D: Reduced serum levels of Vitamin D have been associated with increasing incidence of URTI, but it is not yet clear how this association works. Levels have also been observed to deteriorate following infection, but this could not be explained by inflammatory changes only. It has been hypothesised that increased tissue requirements may be one of the factors responsible. Further studies are required to elucidate the role of Vitamin D in the immune system (46).

In summary, there is no simple biomarker as yet to differentiate between inflammation and infection, and PCT may help to differentiate bacterial from viral infection. Further research is required.

b) Special investigations that may assist with differentiating the aetiology of pharyngitis include:

- **GABHS:** Rapid assays and throat swabs are available to assist in confirmation / exclusion of the diagnosis; sensitivities approach 90% in both investigations, with a possibility of false negatives (47). The total WCC will be raised with a neutrophilic predominance (42).
- **IM:** A moderately raised WCC (12 000 – 18 000), with 60-70% lymphocytes and 10% atypical lymphocytes on peripheral smear are the common findings in a patient with IM. A relative neutropaenia and thrombocytopaenia are often observed. A monospot test (for heterophile antibodies) is specific for IM, but has a poor sensitivity of 75% in the first week of infection, which improves to 95% by the third week. The monospot test has poor sensitivity in children <10 yrs of age. EBV titres for viral capsid antigen may be checked for IgM (indicating acute infection) and IgG (indicating past infection) (42, 47).

c) A diagnosis of myocarditis needs to be excluded

This is not a simple differential diagnosis as a number of complicating factors need to be taken into account and include:

1. Time of year: a high index of suspicion is required, especially in the spring and summer months when enteroviruses are more prevalent – they often present with both respiratory and gastro-intestinal tract symptoms (48).
2. Symptoms on medical history: these range from mimicking an acute MI (chest pain or dyspnoea), dysrhythmias (palpitations), acute congestive failure, syncope, fatigue to no cardiac symptoms at all (49).
3. Physical examination findings: these may include muffled heart sounds, a tachycardia disproportionate to other findings, fever, mitral regurgitation and a pericardial friction rub if pericarditis is present (42). Signs of URTI may be the only presentation as myocarditis may be sub-acute.
4. Resting ECG changes: these may include:
 - Myocarditis: ventricular / supra-ventricular dysrhythmias, ST changes (usually depression), T wave inversion and occasionally left bundle branch block (LBBB) / atrio-ventricular (AV) block (5).
 - Pericarditis: ST elevation may be seen with up-sloping ST segments (in these leads, no T wave inversion) (6).

Note that ECG changes associated with the ‘athletic heart’ should not be misdiagnosed as myocarditis. These include hyperadrenergic T wave changes (which normalize with beta blockade), and early repolarisation changes (49).

5. Blood tests: routine markers of inflammation may be normal in myocarditis (4), therefore further investigations are required: Troponin T/I, and Myoglobin-binding fraction of CK (CK-MB) serum are suggested. Traditionally a CRP and a WCC + differential count are done as well. ESR has been considered non-contributory (7).
6. Echocardiography: transient global left ventricular dysfunction with reduced myocardial contractility and increased LV diastolic dimensions may be seen (4).

2.3. The risk of potential medical complications when exercising at the time of suffering from an acute illness: a review

In this section, the potential medical complications of exercising at the time of suffering from an acute illness will be reviewed. The risk of medical potential complications during exercise is the cornerstone around which safe participation guidelines should be developed. Furthermore, evidence that exercise aggravates the illness should also be considered. It is also acknowledged that the risk of medical complications may depend on a number of factors, including the effects of systemic illness compared with a localised illness, the timing of exercise with respect to inoculation, and the effects of specific organism. Of particular concern is the risk of sudden cardiac death (SCD) during exercise as a result of infective myocarditis or myo-pericarditis, and the potential medical complications when suffering from infectious mononucleosis (IM) and acute gastro-intestinal illness. Finally, the risk of transmission of organisms during exercise is also a factor to be considered in mass sports participation events such as a distance running race.

2.3.1. Potential medical complications of localised compared with systemic illness

Current clinical guidelines regarding exercise participation when an athlete suffers from an acute illness are largely based on the hypothesis that a systemic illness is more likely to result in a medical complication compared with a localised illness. However, there is very little data to support this hypothesis. In a single study, it has been documented that exercise has no effect on symptom severity scores in subjects who were iatrogenically infected with rhinovirus. It is established that rhinovirus infection is localised and does not usually cause a viraemia (50). In this study, 34 moderately fit individuals were randomised to 10 days of 40 minutes of daily exercise at 70% HRR, after inoculation with rhinovirus, and compared with 16 control subjects of similar fitness, who did not exercise. Symptom severity scores (by questionnaire) were assessed every 12 hours, and facial tissue weights were used to measure symptom severity. This is one of the only clinical studies which supports the hypothesis that exercise with localised URTI symptoms is safer compared to exercising with systemic infective illness. To our knowledge, there are no other studies where the risk of medical complications during exercise is shown to be less when athletes suffer from localised compared with systemic illness. This requires urgent study, as the current clinical guidelines are based on this hypothesis.

2.3.2. Potential medical complications related to the timing of inoculation

The timing of exercise related to onset of illness has been investigated in a small number of animal studies. It has been reported that influenza infection increased the risk of death during exercise during the acute phase of an infection (8). There are also data to suggest that exercise during the incubation period of a systemic illness may worsen the severity of the illness (51), and that exercising in the acute phase of illness increases the risk of myocarditis (52). However, we are not aware of any published studies tracking the course of the illness, or the risk of medical complications in athletes with symptoms of acute infection.

2.3.3. Risk of sudden cardiac death (SCD) during exercise as a complication of myo-pericarditis

It has been documented that myo-pericarditis is one of the causes of sudden cardiac death during exercise, particularly in younger athletes (53). Although sudden cardiac death (SCD) is a rare complication of myocarditis, the risk of myocarditis in athletes with acute illness will be briefly reviewed.

2.3.3.1. Aetiology of myo-pericarditis

Myocarditis and pericarditis are characterised by inflammation of the cardiac muscle and pericardium respectively, and often co-exist, thus leading to the term myo-pericarditis. It is usually infective in origin (49). In the past, coxsackie viruses A and B (part of the enterovirus family) were the most commonly implicated viruses in the aetiology of myo-pericarditis (\approx 50% of cases) (49). It has been suggested that selenium deficiency may increase the susceptibility of some populations to myocarditis from these viruses (49). Recently there has been evidence from endomyocardial biopsies that Parvovirus B19 and Human Herpes virus 6 are responsible for more cases of myo-pericarditis than previously thought (54). Other viruses that have been implicated include adenovirus, influenza virus, echovirus, HIV, EBV, CMV and hepatitis C (4-8). Rhinovirus, the most common cause of URTIs, has not been implicated (52). Bacterial causes of myo-pericarditis include **Streptococcus*, *Staphylococcus*, *Pneumococcus*, *Haemophilus* and *Neisseria* (4).

* This has implications for the management of the athlete with a streptococcal pharyngitis.

Atypical bacterial infections have also been reported as a cause for myo-pericarditis. *Mycoplasma pneumoniae* was reported as the responsible organism in 6 % of military recruits with myocarditis (49), and other bacteria include *Chlamydia pneumoniae*, *Borrelia burgdorferi* (Lyme Disease) and *Trypanosoma cruzi* (Chagas' Disease) (49, 52).

2.3.3.2. Epidemiology of myo-pericarditis

There are no epidemiological data on the incidence of myo-pericarditis in athletes presenting with acute illness. In the general population, there are also little data on the actual incidence of myocarditis, as many cases are subclinical. It appears that myo-pericarditis is more prevalent in males, particularly in the 20-40 year age group (42). Pericarditis is most frequently seen in young adults and is the cause of chest pain in 5% of admissions to the emergency department (6). Myocarditis may be the only presentation of an infection or it may be a complication of an apparently localised infection elsewhere *e.g.* URTI, and sub-clinical in nature (*i.e.* no cardiac symptoms) (49), with positive findings in up to 1% of autopsy cases (6).

2.3.3.3. Known complications of myo-pericarditis

The known acute complications of myo-pericarditis include acute cardiac failure, arrhythmias, cardiac tamponade and sudden cardiac death (4, 49). The longer-term complications include chronic heart failure, dilated cardiomyopathy and chronic pericarditis, which may be constrictive in nature (4, 6, 49).

2.3.3.4. Sudden cardiac death (SCD) in athletes and myo-pericarditis

Animal studies

Most of the experimental studies relating acute myo-pericarditis and exercise were conducted in mice inoculated with coxsackie viruses. In these studies, it has been shown that exercise stress in young and adult mice increased inflammation, tissue damage and necrosis. Acute infectious myocarditis was associated with cardiac and skeletal muscle protein breakdown, and viral replication rates were also increased in the suckling mice (49). Exercise stress has been associated with increased mortality in myocarditis (52, 55).

Human studies

In general, the reported incidence of SCD in young athletes varies between 1:44 000 and 1:300 000 (56). Male gender appears to be a risk factor (♂:♀ ratios vary from 5:1 – 9:1) (56), and certain race groups *e.g.* African-American athletes, appear to be at increased risk (56). In a recent review, it has been reported that myocarditis is responsible for 7% of SCD in athletes (56). However, this may vary between 5 and 22% (10).

In one review of sudden unexpected death in 16 young Swedish orienteers before 1992, it was documented that sub-acute / chronic myocarditis was the most frequent finding on histopathology. In this study, near-maximal exercise was implicated in death in all but 2 cases, but only 5 of these cases had reported cardiac symptoms prior to their death (49). These data support the hypothesis that exercise can aggravate sub-clinical (asymptomatic) myocarditis. A case control study reported that a history of a flu-like illness or fatigue in the previous month increased an athlete's odds ratio to 13 for having an acute cardiac event during exercise (57). It must be emphasized that in the majority of cases, myo-pericarditis resolves without sequelae if properly managed and that SCD is a rare event (49). However, from a clinical point of view, it is important to exclude myo-pericarditis before advising an athlete to continue with exercise training or competition.

2.3.4. Exercise-related medical complications of Infectious Mononucleosis

The athlete with acute infectious mononucleosis (IM) may present a particular challenge to the SEM physician. There are several serious medical complications that are associated with IM. The well-documented complication is that of splenic rupture, which may be associated with exercise. Other complications include aplastic anaemia, Guillain Barré Syndrome, meningitis and encephalitis, neuritis, lymphoma, haemolytic uraemic syndrome and disseminated intra-vascular coagulation (DIC) (3). An uncommon complication is airway compromise secondary to tonsillar enlargement. It should be noted that up to 30% of patients with IM have a positive throat culture for *GABHS*.

Splenomegaly is common in patients with IM, with reports of prevalence ranging between 50% (7) and near 100% (3). Splenic rupture is a known, but rare complication of IM, with an estimated incidence of 0.1%-0.2% (3, 33). Splenic rupture may occur with or without co-incident direct

trauma (3). A review of 55 cases of splenic rupture showed that almost half occurred spontaneously, thought to be as a result of sudden increases in portal pressure secondary to a Valsalva manoeuvre (3). Of note was the fact that almost all ruptures occurred in male patients between day 4 and day 21 of infection (33). It is rare that rupture occurs after 4 weeks of infection, indicating that the first 4 weeks constitute a time of increased vulnerability (3).

Clinical examination has limited reliability in detecting splenomegaly (3, 10, 28). Data are limited regarding normative values in athletic populations, some of whom have been shown to have larger spleens than average (an upper limit of normal longitudinal size quoted as 12-14cm) (3).

2.3.5. Risks of medical complications during exercise while suffering from acute gastro-intestinal illness

Acute gastro-intestinal illness, presenting as nausea, vomiting and diarrhoea, is one of the most common acute medical illnesses in athletes. The SEM physician frequently makes a clinical decision on return to play following acute gastro-intestinal illness and therefore the risk of medical complications related to these illnesses is important. Gastro-enteritis may cause dehydration, which in turn may cause electrolyte imbalances and contribute to the development of acute renal failure. Acute diarrhoea is often associated with significant intestinal secretion of fluid (especially *Enterotoxigenic E. Coli*) (47) and these fluid shifts may be associated with hypo- or hypernatraemia, in combination with hypokalaemia (58, 59). Vomiting may also cause a metabolic alkalosis. Changes in ADH levels (related to possible fever as well as fluid shifts) will have consequent effects on serum electrolyte concentrations.

Additionally, the use of medications to provide symptomatic relief in gastro-enteritis may also affect endurance exercise. Anti-spasmodics and anti-motility agents may affect thermoregulation (40), while medications such as loperamide may reduce the passage of diarrhoea, but do not stop the intestinal fluid secretion associated with the illness, thus facilitating a 'hidden reservoir' of lost fluid. This may have implications for fluid homeostasis and thus electrolyte abnormalities.

However, to our knowledge, there are no studies that specifically relate the risk of medical complications to exercising with acute gastro-intestinal illness in athletes. This is a research area that requires urgent attention as RTP guidelines are needed to improve the safety of athletes.

2.3.6. Acute illness and other potential medical complications during exercise

There are a few additional considerations where acute illness during exercise may result in medical complications. Viral infections have been implicated in the development of exertional heat stroke (EHS). The evidence to support this hypothesis comes from two studies that are mentioned in the ACSM Statement on Exertional Heat Illness (60). In one study, 179 ‘heat casualties’ from a 14 km race were documented over a 9-year period: 23% of these runners reported a recent gastro-intestinal or respiratory illness. In the second study, 10 military recruits with EHS were described: 3 had a fever, while 6 had at least one impending sign of illness prior to collapse.

Viral illness has also been associated with the development of acute renal failure (ARF). It appears that the ‘perfect storm’ of conditions may be required for the development of ARF in athletes – a combination of heat stress, dehydration, recent infection, the use of NSAIDs specifically and possible latent myopathies unmasked by the previous-mentioned factors (61). There is also evidence that systemic illness may cause non-exercise-related rhabdomyolysis when unmasking a latent myopathy (62).

2.3.7. Medical complications while exercising with acute illness: the risk of acute illness transmission

One of the considerations in allowing an athlete to RTP, is how contagious they may be, and whether this would present a danger to other athletes. The three main types of infection seen in tournament settings would have remarkably different transmission methods: URTI via droplet or person-person spread (33); gastro-intestinal infection via faecal-oral transmission and consequent poor hygiene / hand-washing practice, or via fomites (63); skin infections such as *herpes gladiatorum* require direct contact. These facts should be considered in a team setting to prevent further transmission, and athletes should be isolated where appropriate.

2.4. Potential effects on performance when exercising with an acute illness: a review

Apart from the risk of medical complications, acute illness may also have negative effects on exercise performance. These data are important in athlete education and for coaching staff, and although this is not the focus of this dissertation, this aspect will be briefly reviewed.

2.4.1. Reduced performance related to infection

There are very few studies where exercise performance during an acute illness has been studied. This is obvious, as there is an ethical issue in performing these studies in humans, given the potential risk of acute medical complications during acute illness. In one study, experimental inoculation of rhinovirus into a healthy college population showed no reduction in pulmonary function, VO_2 max and sub-maximal exercise capacity (50). Rhinovirus is responsible for up to 40% of URTI episodes, making it the most common pathogen (40). Rhinovirus does not usually cause a febrile illness and is usually responsible for localised URTI symptoms. There were some early data to suggest that rhinovirus may cause transient changes in airway reactivity, but these were not clinically significant (64). However, rhinoviruses have been implicated in 60% of exacerbations of “viral” asthma and 59% of exacerbations of “viral” COPD (65), and acute exacerbations of asthma and COPD would have an effect on athletic performance. Systemic infection with influenza viruses is also associated with reductions in pulmonary function (28). In one unpublished study from the 2006 South African Iron Man triathlon, it was shown that respiratory tract symptoms in the 6 weeks prior to the race (especially lower RTS and systemic symptoms) had a significant effect on reducing training volume, and this resulted in slower race times (66).

In summary, there are very few studies in this field. Those studies that are published are not conclusive. To date, to our knowledge, there is no published data that differentiate between localised and systemic pre-race respiratory tract symptoms and how these symptoms impact on the race, in terms of performance and / or post-race symptoms.

2.4.2. Acute illness, bronchial hyper-reactivity and reduced exercise performance

Athletes may present with wheezing after an upper or lower respiratory tract infection (67) and this is a syndrome known as WARI (wheezing after respiratory tract infection). It has been suggested that WARI may potentially have a significant impact on exercise performance in a subset of athletes. It has been documented that up to 40% of patients with community-acquired pneumonia and bronchitis demonstrate transient obstructive airways disease, with a decreased FEV₁. These changes usually last for 3 weeks but can last for up to 2 months (4). However, we are not aware of any data specifically linking WARI to reduced exercise performance in athletes. Most athletes who present with new onset wheezing in a sports setting will have exercise-induced broncho-constriction (EIB) or previously undiagnosed asthma. The incidence of EIB is increased in the athletic population, especially in winter endurance sports such as Nordic skiing and speed-skating, as well as swimmers and summer endurance athletes such as cyclists (35). It has been shown that WARI is increased in athletes whose sports require high minute ventilation rates, which include the above-mentioned sports. However, whether the pathophysiology of WARI is linked to that of EIB and whether this affects performance, is an interesting topic for further study. One study reported an increase in bronchial reactivity in Nordic skiers after a RTI, when compared to non-exercising controls and the conclusion was that the exercise was the responsible mechanism (68). However, this particular subset of athletes is known to be more prone to bronchial hyper-reactivity (35). It is therefore unclear whether the increased bronchospasm was due to infection or the EIB predisposition in the skiers, or a combination of the two.

Organisms that have been implicated in WARI include the ‘atypical pneumonias’ as well as viral infections. *Chlamydophila pneumonia* has been found to be associated with post-infectious reactive airways in all ages (67). There is conflicting evidence of WARI leading to permanent obstructive changes (67). *Mycoplasma pneumonia* has also been associated with WARI in children and adults, as well as asthma recurrence (67). In such atypical infections, macrolide antibiotics appeared to have role in the treatment of WARI, as macrolides have an anti-inflammatory as well as antibiotic effect. However, macrolides have been found to prolong the QT interval, thus increasing the risk of SCD in exercise (7). Viral URTIs can cause wheezing and acute exacerbations in asthmatics, but little evidence exists for this phenomenon in non-asthmatics. The study of rhinovirus inoculation into healthy volunteers showed no changes in

pulmonary function (69). However, this may be virus-specific. RSV is known to cause wheezing, but only in those under the age of 2.

2.4.3. Athlete withdrawal from competition as a consequence of acute illness

An athlete may withdraw from competition as a result of an acute illness. This decision may be made by the athletes themselves, the coach or based on medical advice that an athlete obtained. The days lost as a result of acute illness (time-loss illness) has been reported in some studies. In several multi-day tournaments, the proportion of illness causing a time-loss of ≥ 1 day has been reported to be between 26 and 45% (21-25, 31). Therefore, the proportion of time-loss illnesses in multi-day tournaments is significant for an athlete.

There is not much literature available regarding withdrawal from single events due to illness. However, there are 3 studies of pre-race 'drop-outs' in marathons in the 1980's: the first two reported data from the Aberdeen Milk Marathon, and the third from the Glasgow marathon. The first study reported that illness was responsible for 16% of 502 drop-out responders (response rate of 43%). In this study, a third of runners indicated they would have run a half-marathon if it was an option (70). The second study reported that 12% of drop-outs were as a result of illness, and 73% of these runners decided not to run in the week before the race (71). The third study reported that 46% of drop-outs were due to 'ill-health', which included injury and illness (72). However, in none of these studies was an absolute pre-race drop-out rate reported, as they were based on samples including runners who started and those who did not.

2.5. Decision Modifiers for RTP guidelines

Decision modifiers are only relevant when the participation risk has been ascertained. Modifiers are external influences on the SEM physician's RTP decision, and may increase or decrease the participation risk for a specific athlete with a given health status (1). Traditionally, modifiers in the literature have applied to RTP after injury and include the type of sport *e.g.* lawn bowls does not have the same aerobic requirement as marathon running. The level of competition (amateur *vs.* professional) has been cited as a modifier, as has the importance of the specific event (finals *vs.* heats *etc.*). However, these latter factors should not be considered modifiers in serious

musculoskeletal injury or acute illness. External pressure may also come from coaches and family members, as well as from the athlete themselves (1).

2.6. Available RTP guidelines

Participation guidelines should be able to identify when the athlete is safe to return to training following an illness or an injury. There should be guidance as to the progression of intensity, dependent on symptoms, as well as an indication of when the athlete should be ready to return to competition. The potential risks of exercising while acutely ill have already been discussed. Current recommendations for RTP after acute illness were recently reviewed (7).

Despite the fact that there are several published guidelines regarding RTP in acutely ill athletes, there are relatively few clinical and research data to support these guidelines. Specifically, for URTS, which are one of the most common reasons for presenting to SEM physicians, the evidence to support current RTP guidelines is minimal. Most SEM physicians are guided by the ‘neck check’, which was first described in 1993 (73). The ‘neck check’ is based on self-reported symptoms of acute illness. The RTP guidelines for URTI have since evolved from this first recommendation (7, 8, 28, 33, 42, 49, 64).

In the literature, there are clear evidence-based RTP guidelines available for specific acute illnesses such as myocarditis and infectious mononucleosis (3-8). These guidelines are relevant to the SEM physician as IM is a differential diagnosis for a sore throat / exudative pharyngitis, and myocarditis is a well-publicised risk of exercising whilst ill. However, as mentioned, there are few studies to support the clinical guidelines as outlined in the neck check. Therefore, the basis of the neck check will be reviewed.

2.6.1. The history of the ‘Neck Check’ clinical guideline

The ‘neck check’ guideline was originally proposed in 1993, following a review of the available evidence, mainly from the exercise immunology literature. These data consisted of studies describing the exercise-related changes in immune parameters (73). In this review, the following main conclusions were made:

1. Exercise-related immune changes include an immediate elevation of neutrophils and lymphocytes, mediated by adrenalin. Thereafter a further rise in neutrophils (more in

strenuous exercise) and delayed fall in lymphocytes is seen (cortisol- mediated). NK cell activity and numbers rise during strenuous activity and fall afterwards, returning to normal limits by 24 hours (adrenalin and interleukin-mediated). Decreased concentrations of salivary IgA are seen after strenuous / prolonged exercise. It was recognised that these changes could not be causally associated with clinical infections in athletes, but it was hypothesised that the transient drop in immunity after strenuous exercise may predispose the athlete to developing an URTI.

2. Due to adverse physiological effects of a fever, it was not advisable to exercise with a fever.
3. It was noted, quite rightly, that in the acute phase of an illness, one could not be sure whether the illness would turn into a “harmless URTI, incipient mycoplasmal pneumonia or a virus with a propensity to cause myocarditis”. Additionally, it was emphasised that training in this state would have no benefits, thus REST was advised.
4. Finally, “tentative and arbitrary guidelines” were grudgingly offered for those elite athletes who believed they could not miss a day’s worth of training. This advice was the ‘neck check’. For symptoms ‘above the neck’ *e.g.* runny or congested nose, sneezing or scratchy throat: an athlete could cautiously begin the workout at half speed. If feeling well after 10 minutes, one could complete the workout; if not, the athlete was advised to stop and rest. For fever and symptoms ‘below the neck’ *e.g.* “myalgia, a ‘hacking’ cough, diarrhoea or vomiting”: exercise was not advised.

2.6.2. Current evidence to support the ‘Neck Check’ clinical RTP guideline

The evidence underpinning the neck check clinical guidelines was reviewed 20 years ago and has, to our knowledge, not been reviewed since. Therefore, in the next section of this review Chapter, more recently published evidence to support the neck check guidelines will be reviewed as follows:

- Evidence that it is safe to exercise with localised upper respiratory tract symptoms
- Evidence that there is an increased risk of medical complications during exercise with fever or symptoms ‘below-the-neck’
- Evidence regarding the timescale for RTP after an acute illness

2.6.2.1. Evidence that it is safe to exercise with localised upper respiratory tract symptoms - symptoms ‘above-the-neck’

To our knowledge, the study of iatrogenic rhinovirus infection is the only clinical study that supports the hypothesis that it is safe to exercise with localised upper respiratory tract symptoms. In this study it was reported that exercise stress had no ill effects on severity scores in the subjects (50), and that there was no reduction in pulmonary function (69). This may apply to a rhinovirus infection, which is the most common cause of URTI. However, there are no other data relating to any of the other commonly implicated viruses or other micro-organisms causing URTI. Therefore, with regard to exercising with localised URT symptoms, further evidence of safety is required. However, absence of such evidence does not imply evidence of risk.

There are specific concerns about using a symptom-based ‘neck check’ only. An athlete with a sore throat may have early *GABHS* or IM. In the case of *GABHS*: some authors’ recommendations included clear restriction from play, and suggested rest for the first week of illness, whilst ingesting antibiotics (49). This recommendation was presumably based on the risk of myo-pericarditis from *GABHS*. Some recommendations allow RTP after at least 24 hours of antibiotics and resolution of fever (74). However, diagnosis of *GABHS* requires clinical assessment, and can rarely, if ever, be diagnosed on history alone. IM may also present with only a sore throat. Again, clinical assessment is required to make the diagnosis, and a diagnosis of IM cannot be made on history alone. Furthermore, in the case of IM, RTP guidelines are even more restrictive than those for *GABHS*.

2.6.2.2. Evidence that there is an increased risk of medical complications during exercise with fever or symptoms ‘below-the-neck’

The risk of medical complications during exercise in athletes with acute infections has already been reviewed (Section 2.3). In summary, there is some evidence that fever and symptoms of systemic infections are associated with an increased risk of medical complications during exercise as follows:

- **Fever:**

The adverse effects of fever include metabolic, cardiovascular, musculoskeletal and neuromuscular changes. Increased insensible water losses are seen, together with dehydration and temperature dysregulation (8).

Metabolic changes: these include increased serum levels of adrenaline, causing an increased resting heart rate, a raised metabolic rate and peripheral vasoconstriction. Increased insulin secretion results in lower serum glucose levels (49). ADH levels are reduced, causing increased insensible water losses (8); however, LRTI may cause increased ADH (75).

Cardiovascular changes: these include a tachycardia, reduced stroke volume and aerobic capacity, with some evidence from animal studies suggesting that cardiovascular conditioning may attenuate the reduction in aerobic capacity (49).

- **Myalgia:**

Myalgia is indicative of a muscle dysfunction (40, 49) and may be associated with myositis (76, 77). This may increase the risk of myocarditis, and rhabdomyolysis (61, 62). Reductions in speed, concentration, co-ordination and precision have been noted in febrile illnesses, most evident in days 3-4 of infection (49).

- **Sub-clinical myocarditis:**

Exercise may aggravate sub-clinical myocarditis, which may be asymptomatic from a cardiac perspective (49).

- **Influenza infection (a systemic illness):**

Influenza infection is associated with a reduction in pulmonary function (28). Animal studies with influenza infection showed increased lethality in the acute phase (8). It is unclear whether the risks are a function of the organism, or the systemic nature of the illness.

- **Gastro-enteritis:**

The potential risk of medical complications during exercise in athletes with gastro-enteritis has been reviewed in Section 2.3.5. These risks include dehydration and electrolyte abnormalities, as well as the effects of the medications commonly used in these infections.

- **LRT symptoms:**

The presence of a fever may be a guide to diagnosing pneumonia, but there are no published data that we are aware of which detail the risks of exercising with LRTI. However, exercise is a known aggravating factor in asthma, and increased bronchospasm and dyspnoea could therefore be expected when these athletes develop a LRTI. In an athlete presenting with a productive cough, but no systemic symptoms, a diagnosis of bronchitis (mostly of viral

origin) has to be considered. However, there is no evidence that reports on the effects of exercise in bronchitis (42). As mentioned previously (Section 2.4.2), some athletes with LRTS may have WARI, but there is no data as yet to indicate whether exercising with WARI is safe, or whether it affects performance. Further studies are required in this field.

2.6.2.3. Evidence regarding the timescale for RTP after acute illness

There are few clinical and research data concerning a safe timeframe for RTP. Instead, there has been an evolution of current recommendations regarding the timescale for RTP following an acute illness. This can be summarised as follows:

- It has been shown that illness may be exacerbated if an athlete exercises in the acute infective stage (51). Therefore, in 1996, it was suggested that training be reduced for 2-3 days before intense exercise is resumed in patients who feel they are getting ill, in order to prevent aggravation of the illness (40).
- In 2000, these recommendations were consolidated in a statement indicating that serious illness often has prodromal symptoms and may take 2-3 days to declare itself (49).
- In 2007, clinical data were published to support this recommendation. In this study, it was documented that symptom and functionality scores were significantly lower on days 3-4 in triathletes in whom an infective organism had been identified (16).

2.6.3. Summary: Evidence to support current recommendations regarding RTP guidelines for athletes with acute illness

In this section, data that are relevant to RTP guidelines for athletes with acute illness have been reviewed. It is clear that there are very few clinical or laboratory studies in this field. Despite the lack of clinical data, there have been many published recommendations, including position statements by the British Association of Sports and Exercise Science (BASES) in 2005 (78, 79) and the more recent International Society of Exercise and Immunology (ISEI) in 2011(10).

The following is a summary of the current recommendations on RTP guidelines for athletes with acute illness, since the original neck check was proposed more than 20 years ago:

- In athletes presenting with initial symptoms of illness, the presence of a fever or any systemic symptoms such as arthralgia, myalgias, headache, diarrhoea or vomiting should preclude

them from any exercise (10, 78).

- Athletes should refrain from strenuous exercise in the early phase (first day) of infection, and may gradually increase their intensity over a few days if their symptoms remain ‘above-the-neck’ (e.g. runny nose, scratchy throat). Athletes should preferably exercise alone to prevent transmission of the illness (10, 78).
- It was recommended that a temperature of 0.5 - 1°C higher than normal baseline, together with a heart rate of 10 beats per minute above the normal resting HR, as well as systemic symptoms (fatigue, muscle tenderness or pain, arthralgia or headache) all indicate that the athlete should rest from exercise until systemic symptoms have resolved (49). This statement presumes that the athlete knows their resting HR and baseline body temperature. It has been suggested that athletes measure their resting HR, as there is some evidence in swimmers that an increase in both supine and standing values may indicate the onset of an illness (41).
- Athletes should present early to their team physician if part of a team, or travelling, for the benefit of their own and the team’s health (21).
- The diagnosis of *GABHS* pharyngitis precludes the athlete from participation, for between 1-7 days, depending on the recommendations followed (49, 74).
- Athletes with influenza should refrain from exercise for at least 5 days (to allow for infectivity to clear), before returning at light intensity exercise. This RTP is dependent on the absence of fever for at least 24 hours and the resolution of systemic symptoms (4, 79).
- Athletes with confirmed or suspected pertussis should be isolated for the first 5 days after symptoms begin (4).
- In the return to exercise training, it should take as many days as the athlete was not training, to increase exercise intensity to the pre-illness level (10, 64, 78).
- In the case of athletes with URTI or GI symptoms, the athlete has to be free of fever for at least 1 day following the URTI / GI symptoms before light exercise may be undertaken (10, 78).
- For gastro-intestinal infection, RTP may only be considered once symptoms and fever have resolved and body weight is normal or near-normal after adequate rehydration. If blood tests were done, serum electrolyte concentrations, haematocrit, liver function and inflammatory markers must all have returned to normal (7, 10, 78).
- If returning to exercise post-URTI and exercising in temperatures of < -10°C, cold air protection should be used for at least a week, to prevent any aggravation of WARI (10, 78).
- If initial symptoms worsen, fever recurs, cough worsens or breathing problems arise during exercise, a medical opinion should be sought (10, 78).

- Inflammatory markers must return to normal before RTP is considered (7).
- A resting ECG is advised before RTP when an athlete used a macrolide antibiotic – this is due to the risk of prolonged QT Syndrome with these antibiotics and consequent risks of SCD during exercise (7).
- The ISEI statement also includes a recommendation for any elite athlete with a non-specific URTI to not exercise for 4 weeks afterwards, with a view to preventing myocarditis. It recognizes that this recommendation will rarely be followed, but urges the clinician to have a high index of suspicion of myocarditis in the spring or summer, when viral infections such as Parvovirus B19, Echovirus, coxsackie virus and Herpes Virus 6 are more prevalent (10).
- There are inadequate data regarding RTP after LRTI, including bronchitis, with a general recommendation to see a physician to ensure full resolution of symptoms (4, 7, 55, 75). Following the ISEI guidelines, athletes may only RTP once their fever and systemic symptoms resolved (4, 7, 55, 74, 75). In the case of WARI, there is no evidence as yet to indicate safe parameters for RTP. There are some guidelines for RTP after EIB, but these only apply to those athletes who develop EIB acutely during exercise (80).
- There are clear recommendations for athletes returning to play after a diagnosis of IM in order to reduce the risk of splenic rupture. These guidelines have been extensively described in the literature (3, 7, 10, 28, 33).
- The 36th Bethesda Conference gives clear recommendations for a minimum of 6 months off competitive exercise before RTP following a diagnosis of myocarditis and pericarditis (5). The previously mentioned study of SCD in young Swedish orienteers reported a marked reduction in SCD after 1992, at which time the 6-month exclusion recommendations were introduced (49).

In summary, several authors or official bodies have provided guidelines on RTP for athletes with acute illness. However, this review shows that these guidelines are an extension of the original ‘neck check’, with few recent clinical or laboratory studies to support the current guidelines. There are very few data to support the safety of exercise with a localised URTI; however, the near-absence of evidence of safety does not imply evidence of risk and further studies are therefore indicated. Excluding the clinical data regarding myocarditis and splenic rupture in IM, there are few clinical data examining the risks of exercising with LRT or systemic symptoms.

It is also clear from the review that a RTP guideline cannot be used on the basis of a patient’s reported symptoms only. At the very least, a clinical assessment (including a physical

examination) is essential for these guidelines to be implemented safely. Athletes should be examined at the initial assessment, as well as before RTP to ensure that clinical resolution of symptoms has occurred.

2.7. Summary

In summary, the aim of this literature review was to establish the evidence base behind current return-to-play (RTP) guidelines for athletes with acute illness.

There are no clinical data to correlate the exercise-related changes in immune parameters with symptoms of upper respiratory tract infections commonly seen in athletes. There are few data pertaining to pre-competition prevalence of acute illness. The available evidence refers to the incidence rate of illness in tournament settings, where symptoms of URTI are very common, followed by gastro-intestinal and skin infections. Post-race URT symptoms may be related to pre-race symptoms, which may not be infective in origin, and allergy needs to be considered as one of the possibilities.

Possible risk factors for acute illness in the pre-competition period included an increased training load, where a 'J-curve' and 'S-curve' have been described with reference to URTS in elite and high-load athletes. There are no conclusive data regarding the effect of gender on illness risk, although some studies show a slight increased risk in females. Similarly, some studies show no difference in risk associated with age, whereas others report an increased risk with older age. Travel has been reported to increase the risk of infection, with closer proximity of team-mates, food-borne gastro-enteritis and other unknown factors at destinations more than 5 hour time zones away from home, being cited as risks. Allergy is a documented risk factor for URTS, as is environment, with cold-weather sports with high ventilation volumes being at significant risk. Different sporting codes have reported differing incident rates of illness.

Current recommendations regarding RTP following acute illness refer to symptomatology only. The contribution that a clinical assessment would provide in the RTP decision-making process was discussed. The clinician has an important role in interpreting symptom complexes, whilst considering allergy as a differential diagnosis in URTS. Objective parameters on examination were described with respect to infection, such as increased body temperature and heart rate. Clinical assessment is poor at differentiating infective from non-infective symptoms, and it is

difficult to differentiate between bacterial and viral infections. Laboratory investigations may improve this process, but most of the investigations are non-specific for infection *vs.* systemic inflammation *e.g.* ESR and CRP. Research is being directed at novel biomarkers of infection *e.g.* PCT, but these mostly target sepsis, which is bacterial in nature. Currently, there are no biomarkers that differentiate between inflammation, viral infection and bacterial infection.

There is evidence for the potential complications of exercising with symptoms of acute infection. SEM physicians need to be aware of this information to be able to make an informed decision regarding safe RTP. There are some clinical data documenting the adverse effects of fever: these include metabolic, cardiovascular, musculoskeletal and neuromuscular changes. Additionally, increased insensible water losses occur, resulting in possible dehydration. Temperature dysregulation occurs with febrile illness. These changes all put the febrile exercising athlete at risk for complications. Other potential medical complications include exacerbation of the illness, possibly related to the timing of exercise with respect to timing of inoculation. Furthermore, there is a risk of sudden cardiac death when exercising with myo-pericarditis. When exercising with IM, the main risk is splenic rupture, seen mostly in males in the first 3 weeks of infection. Other potential complications include dehydration and electrolyte disturbance in gastro-enteritis and viral illness may increase the risk of acute renal failure and exertional heatstroke.

There are few data regarding acute illness and performance, but some data do suggest that performance may be sub-optimal in athletes with acute illness, either due to the illness itself or sequelae such as WARI. A significant adverse effect of illness on performance is the potential withdrawal from competition.

Finally, all the available evidence was correlated with the current recommendations on RTP after acute illness, the so-called 'neck check'. The original recommendations by Eichner were examined – these were based on studies detailing immune changes in athletes after exercise, as well as those physiological changes seen with fever. Each aspect of his recommendations was evaluated as to whether there have been any further contributions in the literature, which support or refute his advice. To date, there is only one clinical study to support the safety of exercising with a localised URTI *i.e.* 'above the neck' symptoms, caused by rhinovirus. There are no clinical data to suggest that exercising with such localised URTI symptoms is associated with an increased risk of medical complications. There is some evidence to support the hypothesis that exercising with systemic or 'below-the-neck' symptoms poses a wide variety of risks to the

athlete. By necessity, many of these data are epidemiological in nature, and there are few clinical studies. Despite this lack of data, many authors and official bodies have published guidelines, each of which is an extension of former recommendations, with little new data to support them. In the last 20 years there is little additional evidence to support the use of the ‘neck check’ as a participation guideline in athletes after acute illness. Infectious mononucleosis and myo-pericarditis are the only conditions where clearer, evidence-based RTP guidelines are available.

It has therefore clear that there is insufficient evidence to address many of the questions that were raised in the Introduction section of this dissertation. Therefore, a prospective study was undertaken in a cohort of runners who presented with acute illness before a distance running event and this will be reported in Chapter 3 of this dissertation.

Chapter 3: Original research study

Illness, adherence to medical advice, and participation data in 242 endurance runners presenting to a Pre-Race acute Illness Medical Assessment (PRIMA) facility – a prospective cohort study

3.1. Introduction

In Chapter 2, the relationship between acute illness and exercise was reviewed, specifically with the view to provide safe participation advice to an athlete with symptoms of acute illness. There is good evidence that symptoms of URT illness constitute the most common reason for medical consultations in SEM clinics (16, 47), as well as in tournament settings (20-24, 31). These symptoms may not always be infective in origin and a different aetiology such as allergy should be borne in mind (12, 13, 16, 18). Training load (16, 26, 29, 30), environment (24, 35, 36), travel to a distant country (32) and allergy (17) have been identified as significant risk factors for such symptoms.

There is also a risk of acute medical complications during exercise in athletes with an acute illness. It is essential to determine this risk, and provide safe participation guidelines (1). The risk of medical complications is related to a number of factors including the nature of the illness (localised or systemic symptoms), presence of fever (8), the risk of myocarditis (52, 54), and possible splenic rupture up to 4 weeks following infection with infectious mononucleosis (3, 33). Furthermore, there is scant clinical evidence in humans regarding the effect of exercise on the course of illness (50), and there are few clinical data examining the effect of acute illness on exercise performance (66). In some studies, time-loss as a result of acute illness has been documented (21-25, 31).

Currently, the RTP guideline for athletes with acute illness is the ‘neck check’. The available evidence supporting the neck check as a participation guideline in athletes with symptoms of acute illness, both in terms of its validity and application has been reviewed (Chapter 2). From this review, it is clear that there are minimal data supporting the safety of exercising with localised URT infection, *i.e.* ‘above-the-neck’ illness (50, 69). There are some data to support the potential risks of exercising with ‘below-the-neck’ illness (8, 28, 64). The only clinical data

regarding a timeline for RTP suggest that functionality and symptom scores are lowest on days 3 and 4 in athletes with proven infection (16). To our knowledge, there are no studies examining the application of the neck check principles for guiding safe participation; neither are we aware of any studies exploring what happens to athletes who participate when they do have a clinical diagnosis suggesting acute illness.

We are also not aware of any data documenting the point prevalence of acute illness (based on clinical examination) before an endurance event. In previously published studies, the prevalence of symptoms of illness before athletic events has been based on self-reported symptoms only (15, 17, 30, 81). However, there is evidence that a physical examination of an athlete with symptoms of acute illness is important to make an accurate diagnosis and thereby optimise management (Chapter 2).

The Old Mutual Two Oceans Marathon takes place in autumn in Cape Town, South Africa. A 56km ultra-marathon and half-marathon are the main events, with trail runs of 10 and 21km offered as smaller events, together with a 9-10km fun run. In 2012, a pilot project was undertaken whereby elite and recreational half-marathon and ultra-marathon runners could obtain free medical advice at a **Pre-Race acute Illness Medical Assessment (PRIMA)** facility during race registration in the 3 days prior to the race. The feasibility for runners to be assessed clinically and then advised on safety to participate was tested in this pilot project. The PRIMA was based on a modified 'neck check', as summarised in the current RTP guidelines (7, 9, 49, 73, 78). Athletes were given advice, based on a medical history only, or a medical history and a physical examination. Based on the outcomes of this pilot project, we planned this study to investigate the athletes with pre-race symptoms of acute illness, the use of the neck check as a participation guideline as well the tracking of such a cohort with respect to race participation, race completion and possible medical complications during exercise.

3.2. Aim of the study

The aim of this study was to 1) document the type and prevalence of acute illness in runners presenting to a Pre-Race acute Illness Medical Assessment (PRIMA) facility in the 3 days before a race, 2) determine adherence to advice given by medical staff to runners with acute illness, 3) determine the effects of the outcomes of the medical assessment on the ability to finish the race, and 4) determine the effects of the outcomes of the medical assessment on medical complications

during the race. These data are important to improve the medical care of runners (and other athletes) presenting with acute illness before training and competition.

3.3. Methodology

3.3.1. Type of study

This was a prospective cohort study.

3.3.2. Pre-Race acute Illness Medical Assessment (PRIMA) facility

A ‘Medical Village’ at the compulsory registration venue provided an opportunity to establish a Pre-Race acute Illness Medical Assessment (PRIMA) facility, where runners, who were concerned about symptoms of acute illness, could be assessed free of charge.

The PRIMA facility was advertised in educational health emails that were sent out to all registered runners in the 3 months before the race, as well as in the event magazine. In 2013, a pre-race information booklet regarding acute illness was sent by email to all registered runners in the week preceding the race. The email invited them to the medical facility in case they had any concerns regarding acute illness. In 2014, runners received a text SMS message 6 days and again 4 days before the race, inviting them to the medical facility in case of any concerns regarding acute illness. Staff at the registration venue could also direct runners to the medical facility. Several runners with symptoms of acute illness were also sent to the medical facility from the main sponsor’s stall, where free ‘wellness checks’ for blood pressure, cholesterol and glucose were on offer. The PRIMA facility was open for the duration of the Registration Expo in the three days prior to the race and was also advertised in the registration venue, and was staffed by Sport and Exercise Medicine (SEM) physicians as well as nursing staff.

3.3.3. Pre-Race acute Illness Medical Assessment (PRIMA)

Runners could present themselves to the PRIMA facility without an appointment. Upon presentation, staff screened all the runners (doctors only in 2013, and either nurses or doctors in 2014). Screening consisted of obtaining demographic data, followed by obtaining a standardised medical history. A standardised physical examination was advised, if indicated by elements in the

history (see section 3.3.3.1. below). Runners were assessed 3 days before, 2 days before or 1 day before the race. All data were recorded on Samsung electronic tablets. Demographic information included the runner's name, gender and unique race number, as well as the race for which they were registered. Details of the PRIMA are shown in Appendix A.

3.3.3.1. Medical history

A medical history was taken with the focus on the runner's main presenting symptom and any secondary symptoms. On the basis of this medical history, the runner was advised to undergo a physical examination. The presence of any one (or more) of the following symptoms triggered the advice that a physical examination is indicated:

- Any systemic symptoms including a history of fever, myalgia, general body aches, excessive fatigue, malaise, arthralgia, or headaches.
- Any lower respiratory tract symptoms including a productive or non-productive cough, wheezing, "tight" chest, chest pain or shortness of breath.
- Any gastro-intestinal symptoms including abdominal pain, cramps, nausea, vomiting, or diarrhoea.
- Any cardiac symptoms including chest pain, shortness of breath, or palpitations.
- A sore throat.
- Any runner requesting a physical examination.

3.3.3.2. Physical examination

Prior to a physical examination, informed consent was obtained. The physical examination was performed in a private area by one of the physicians. In 2014, the nurses performed the following vital sign investigations: aural thermometry (using one Braun aural thermometer), resting blood pressure, and resting heart rate. Following a general examination, a specific systemic examination was performed as indicated, and consisted of examination of the following systems: ear, nose and throat (ENT), respiratory, cardiac, abdominal, neurological or musculo-skeletal systems. All clinical data (medical history and physical examination) were recorded in the same file and stored securely. The final working diagnosis was recorded, together with any secondary diagnoses.

Any runner with any upper or lower respiratory tract symptoms, gastro-intestinal symptoms or systemic symptoms (fever, fatigue, malaise, myalgia, arthralgia, general body aches, headaches)

were assessed. Symptoms of other localised infections were also included. Two clinicians decided if there was a possible infective component by reviewing the data from runners. Data included the symptoms as well as the working diagnoses recorded by the treating physicians. In cases where it was not clear that there was an infective aetiology, body temperature and heart rate were taken into account. Tympanic temperature was considered to be above normal if ≥ 37.5 °C in males, and ≥ 37.1 °C in females (as referenced in (82)). A resting HR of >75 was used as an indicator of possible infection, in the context of appropriate symptoms. A sinus bradycardia (<60 beats / min) is seen in up to 80% of trained endurance athletes (83) and the resting HR is known to increase by 10-15 beats / min with illness (41). Where a discrepancy was noted between clinical findings and working diagnosis regarding infection as a possible aetiology, a working diagnosis was made by the treating clinician. Examination findings were evaluated for abnormalities that would suggest infection, or for changes associated with non-infective aetiologies such as allergies.

3.3.3.3. Diagnostic groups

Following the PRIMA assessment, and based on the final clinical diagnosis, runners were therefore categorised into those with a clinical diagnosis of an infection (PRIMA infection group: PRIMA-I), or those runners with no evidence of an infection (PRIMA non-infection group: PRIMA-N/I).

In the PRIMA-I group, diagnostic codes were assigned to each runner and categorised as either 'Localised' (L) or 'Systemic' (S). Localised URTI included: rhinitis (infected or not infected); pharyngitis; laryngitis; sinusitis and other localised infection. These illnesses were considered to be "above-the-neck" and constituted a 'passed' 'neck check'. Where cervical lymphadenopathy was noted to be present with localised throat erythema, it was considered to be a localised pharyngitis that passed the neck check, as long as no exudate or systemic features were noted. The original 'neck check' advice made no mention of localised lymphadenopathy (73).

Systemic illness included the following: URTI with systemic features; systemic infective illness (mostly 'flu'-like illnesses); suspected myo-pericarditis; LRTI and gastro-enteritis. These illnesses were considered to be "below-the-neck" and constituted a 'failed' 'neck check'. In cases where two diagnoses were recorded and both were localised infections, the primary diagnosis was used. However, if the primary diagnosis was a 'localised' illness and the secondary diagnosis was systemic in nature, the secondary diagnosis was used.

Runners with non-infective pathologies were assigned diagnostic codes indicating cardiac, musculoskeletal (MSK), lower respiratory tract symptoms of non-infective origin (LRTS) and ‘Other’ pathology. These runners comprised the PRIMA-N/I cohort.

3.3.4. Advice given to runners in the PRIMA group

On completion of the PRIMA, medical staff gave runners advice regarding participation on race day. There were three main possible outcomes for the advice given to runners. For runners in the PRIMA N/I group, appropriate advice was given, based on their clinical diagnosis (non-infective). In the PRIMA I group, the advice was based on the principles for current RTP clinical guidelines using the ‘neck check’.

3.3.4.1. Advice not to run (ANR)

Runners were advised not to run on race day if they presented with “below the neck” or systemic features of illness, including any of the following:

- Any systemic features of illness (fever, tachycardia, myalgia, excessive fatigue).
- Any symptoms of gastro-enteritis, namely diarrhoea and vomiting, or clinical evidence of dehydration.
- Any lower respiratory tract symptoms or signs, namely cough, wheeze, shortness of breath, chest pain, or any abnormal respiratory finding compatible with infection.
- Pharyngitis suspected to be of *GABHS* origin (‘Strep throat’) including exudative tonsillo-pharyngitis.
- Any other condition, infective or otherwise, where the clinician felt it would not be advisable to compete.

3.3.4.2. Advice to monitor symptoms and handing out an information sheet with return to play information and guidelines (Info+MS group)

As previously indicated, runners were assessed up to 3 days before the race. Therefore, runners who had symptoms more than 24 hours before the race were in some instances advised to monitor their symptoms, and then use the information and guidelines to decide on race day whether to compete or not. These runners were given one or more of three educational information leaflets on ‘Exercise and acute illness’, ‘Exercise and URTI’ or ‘Exercise and gastro-intestinal infection’

(Appendix B). The information in the leaflets was discussed so that the runner could make an informed decision on race day. This advice was based on the ‘above-the-neck’ symptoms mentioned in the neck check.

3.3.4.3. Advice that it is probably safe to participate, together with handing out an information sheet with return to play information and guidelines (Info only group)

Runners who had very localised URTS, with no evidence of systemic features, were advised that it was probably safe to race. These runners were advised to see how they felt after the first 10-15 minutes of the race, starting at a pace 50% slower than usual. If they felt fine, it was deemed safe to continue. However, they were advised to stop running and withdraw from the race if their symptoms deteriorated. All these runners were also given the same educational information leaflets (section 3.3.3.3), and this information was discussed with them.

3.3.5. Research Ethics and Informed consent

This study formed part of a large prospective cohort study on reducing the risk of medical complications in endurance sports. This study is titled: “*Medical consequences in endurance sports. Two Oceans Marathon longitudinal study: 2013-2015*”. Research Ethics approval for this study was obtained from the Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town prior to starting the study (REC: 441/2012) (Appendix C).

3.3.6. Study participants and demographics

All the runners who registered for the 56km or the 21km races in the 2013 and/or the 2014 Old Mutual Two Oceans Marathon in Cape Town, South Africa were considered as possible study participants. In this study, 53 976 runners were registered for the 2 races in 2013/14, of which 242 were seen in the medical facility for a PRIMA consultation. Of these 242 runners (PRIMA group), 172 had symptoms suggesting acute illness and comprised the PRIMA-I study cohort (n=172). Those runners with diagnoses of a non-infective aetiology comprised the PRIMA-N/I group (n=70). The control group of runners for this study comprised the remaining runners who did not present to the PRIMA facility at registration (CON=53 734).

The demographic data for the runners in all the study groups by gender, and by race type (ultra- and half-marathon) are depicted in Tables 3.1a, Table 3.1b, and Table 3.1c.

Table 3.1a. Demographic data by gender of the runners in the study groups

	CON group		PRIMA group		PRIMA-I group		PRIMA-N/I group	
	N	%	N	%	N	%	N	%
Male	31 489	58.5	158	65.3	100	58.2	58	82.9
Female	22 315	41.5	84	34.7	72	41.8	12	17.1
Total	53 734	100	242	100	172	100	70	100

In this study, the PRIMA-I group forms the main cohort and outcome variables will be compared between this group and the CON group. There was a similar gender distribution in the PRIMA-I group compared with the CON group.

Of the 21 343 runners in the CON group registered for the ultra-marathon, 15 508 (72.7%) were male, and 5 835 (27.3%) were female. In the PRIMA-I cohort of 66 Ultra-marathon runners, 52 (78.8%) were male and 14 were female (21.2%) (Table 3.1b.). Therefore, the proportions of runners in the PRIMA-I and CON groups registered for the ultra-marathon were similar.

Table 3.1b. Demographic data by gender of the ultra-marathon runners in the PRIMA and PRIMA-I study groups

	CON group		PRIMA group		PRIMA-I group	
	N	%	N	%	N	%
Male	15 508	72.7	80	77.7	52	78.8
Female	5 835	27.3	23	22.3	14	21.2
Total	21 343	100	103	100	66	100

Of the 32 391 runners in the CON group registered for the half-marathon, 15 932 (49.2%) were male, and 16 459 (50.8%) were female. In the PRIMA-I cohort of 106 half-marathon runners, 48 (45.3%) were male and 58 (54.7%) were female (Table 3.1c.). Therefore, the proportions of runners in the PRIMA-I and CON groups registered for the half-marathon were similar.

Table 3.1c. Demographic data by gender of the half-marathon runners in the PRIMA and PRIMA-I study groups

	CON group		PRIMA group		PRIMA-I group	
	N	%	N	%	N	%
Male	15 932	49.2	69	49.6	48	45.3
Female	16 459	50.8	70	50.4	58	54.7
Total	32 391	100	139	100	106	100

3.3.7. Main measures of outcome

There were six measures of outcome in this study.

3.3.7.1. Prevalence of the clinical diagnosis of runners with non-infective acute illness (PRIMA-N/I group)

The point prevalence rate (% runners) of final diagnosis in the PRIMA-N/I cohort will be reported.

3.3.7.2. Prevalence of reported symptoms and clinical diagnosis of runners with acute infective illness

The point prevalence rate (% runners) of symptoms, and the final diagnosis of acute infection in the PRIMA-I cohort will be reported. In addition, the prevalence of runners (%) in the PRIMA-I group who failed the ‘neck check’ will be reported.

3.3.7.3. Advice given to runners with acute infective illness

The advice given to runners will be reported as % runners with a) advice not to run (ANR), b) advice to monitor symptoms and information given (Info+MS), and c) information only given (Info only).

3.3.7.4. *The incidence of not-starting the race (per 1000 runners) ('Did not start' rate: DNS rate)*

All runners were tracked during race day using an electronic chip that was attached to one of the shoes of the runner. All runners crossed mats at the starting line, along the route and at the finish line where the data in the chip was identified and recorded. A runner was categorised as 'not-starting' if:

- A start time was not captured from the 'Champion-chips' on the start-line mats.
- A split time was not captured from the 'Champion-chips' on the course mats.
- A finishing time was not captured from the 'Champion-chips' at the finish.

3.3.7.5. *The incidence of not-finishing the race (per 1000 runners)('Did not finish' rate: DNF rate)*

All runners were tracked during race day. A runner was categorised as 'not-finishing' if:

- A runner started, but no finishing time was not captured from the 'Champion-chips' at the finish line.
- A runner started but made use of the medical facilities on the course and did not finish the race.

3.3.7.6. *The incidence of medical complications during or immediately after the race (per 1000 runners) ('Medical complications' rate: MC rate)*

All runners were tracked during race day. A runner was categorised as 'medical complications' if:

- A runner started but was admitted to the medical facility at the finish.
- A runner started but made use of the medical facilities on the course and did not finish the race.

The procedure for data capture of all medical complications in runners of the Two Oceans race has been described (84).

All the outcome measures were analysed in the CON group, the PRIMA group and the PRIMA sub-groups (PRIMA-I, and PRIMA-N/I).

3.3.8. Statistical analysis of data

All data were entered into an Excel spreadsheet (Microsoft 2010) and analysed using the SAS (V9.3) statistical package (SAS Institute Inc, Cary, North Carolina, USA). Most of the data were analysed in two-way tables, using two-tailed Chi-square tests with Yates' correction factor to calculate p-values. In some cases, numbers were too small with <5 data in a field; a Fisher's exact test was then used to calculate probability values of p. P-values of <0.05 are considered statistically significant.

3.4. Results

3.4.1. Prevalence of the clinical diagnosis of runners with non-infective acute illness (PRIMA-N/I group)

The PRIMA N/I cohort consisted of 70 runners, and the prevalence of the final diagnoses of non-infective aetiology in this group is depicted in Table 3.2.

Table 3.2. Final diagnoses in the PRIMA-N/I cohort (n=70)

Diagnosis		Number	%
Total		70	100
Cardiac	Arrhythmias	3	4.3
	Hypertension	9	12.9
MSK		23	32.9
LRTS		9	12.9
Other		26	37.1

Most runners in this group presented with 'other' conditions (37.1%). Amongst others, these included pregnant runners with concerns, and runners with non-specific medical concerns. The most common specific group was musculo-skeletal conditions (32.9%), followed by hypertension (12.9%) and non-infective lower respiratory tract conditions (12.9%).

3.4.2. Prevalence of symptoms and clinical diagnosis of runners with acute infective illness and the neck check results (PRIMA-I group)

3.4.2.1. Prevalence of symptoms in the PRIMA-I group

The PRIMA-I group comprised 172 runners (0.32% of all race registrants) and the prevalence of symptoms reported by athletes in this group is depicted in Table 3.3.

Table 3.3. The prevalence (% in runners) of all reported symptoms in PRIMA-I cohort

Symptom	Number	%
Sinus congestion	69	40.1
Sore throat	65	37.8
Runny nose	44	25.6
Cough - non-productive	33	19.2
Cough - productive	33	19.2
Fever	23	13.4
Fatigue	22	12.8
Other	14	8.1
General body aches	13	7.6
Headaches	13	7.6
Tight chest	11	6.4
Myalgia	10	5.8
Shortness of breath	9	5.2
Earache	8	4.7
Abdominal cramps	7	4.1
Chest pain	5	2.9
Diarrhoea	4	2.3
Nausea	4	2.3
Dysuria	1	0.6
Arthralgia	1	0.6
Abdominal pain	1	0.6
Haematuria	1	0.6

The most common symptoms (suffered by >10% of runners) were sinus congestion (40.1%), followed by cough (38.4%, but divided between productive and non-productive types evenly), sore throat (37.8%), runny nose (25.6%), fever (13.4%) and fatigue (12.8%). Runners could report more than 1 symptom, and some reported up to 8 symptoms.

3.4.2.2. The final diagnoses in the PRIMA-I group

The final diagnosis based on clinical assessment (either medical history only (MHO) or medical history and physical examination (MH+PE)) of runners in the PRIMA-I group is depicted in Table 3.4.

Table 3.4. The final diagnosis after clinical assessment in the PRIMA-I group (n=172)

Diagnosis			N MHO	N MH+PE	Total N	%	Cum %
All			11	161	172	100	
Localised Illness	URTI	Rhinitis – (n-i)	1	27	28	16.3	16.3
		Rhinitis– (i)		2	2	1.2	17.5
		Pharyngitis	2	28	30	17.4	34.9
		Laryngitis		3	3	1.7	36.6
		Sinusitis	6	30	36	20.9	57.5
	Other localised infection		2	2	1.2	58.7	
Systemic illness	Generalised URTI		1	38	39	22.7	81.4
	Syst. infective illness			4	4	2.3	83.7
	Possible myocarditis			1	1	0.6	84.3
	LRTI			18	18	10.5	94.8
	Infective gastro		1	8	9	5.2	100

Of the 172 runners in the PRIMA-I cohort, 99 (57.5 %) had a diagnosis of a localised URTI, and 2 had a localised other infection. Of the localised URTI, the most common diagnosis was sinusitis (20.9%), followed by pharyngitis (17.4%) and non-infective rhinitis (16.3%). 71 (41.3%) runners had an illness of a systemic nature. The most common diagnosis was URTI with generalised symptoms (22.7%), which was the single most common diagnosis in the entire group. The next most common diagnosis was LRTI (10.5%).

3.4.2.3. The neck check status of runners in the PRIMA-I group

In the PRIMA-I group, 101 runners passed the neck check (58.7%), whilst 71 failed the neck check (41.3%). The proportions differed on the different days that runners were evaluated before the race (Table 3.5.). The percentages refer to the percentage of the whole PRIMA-I group.

As the delay before the race diminished, increasing proportions of runners were evaluated in the PRIMA facility. Almost half (49.4%) of runners were evaluated the day before the race, during which the largest proportion of neck check failures (46.5%) were also evaluated.

Table 3.5. The neck check status of runners in the PRIMA-I cohort (all days, and in the 3 days before to the last day just before the race) (n=172)

<u>Day</u>	<u>Pass</u>		<u>Fail</u>		<u>Total N</u>		<u>p-value^a</u>
	N	%	N	%	N	%	
Total	101	58.7	71	41.3	172	100	0.0277
Race -3:	14	8.1	16	9.3	30	17.4	0.2092
Race -2:	35	20.4	22	12.8	57	33.1	0.386
Race -1:	52	30.2	33	19.2	85	49.4	0.0205

Race -3 refers to 3 days before the race, and Race -1 refers to the day before the race

^a p-value calculated for passing / failing neck check and MH+PE vs MHO.

3.4.3. Advice given to runners with acute infective illness

The advice given to runners was as follows: a) advice not to run (ANR), b) advice to monitor symptoms and information given (Info+MS), and c) information only given (Info only). An outcome of ‘Other’ was assigned to runners who were given prescriptions for medication or non-urgently referred to other health professionals, but where the advice in the record was not clear with respect to safety of participation.

In the PRIMA-I group, 11 runners were given advice after a medical history only (MHO): 3 were given information only, whilst 8 were also advised to monitor symptoms. The remaining 161 runners in the PRIMA-I group were assessed by a medical history as well as physical examination (MH+PE). The advice given to these athletes is depicted in Table 3.6 with reference to the day they were seen.

Table 3.6. Advice given to runners after MH+PE (n=161)

<u>Day seen</u>	<u>ANR</u>	<u>Educational information</u>		<u>Other</u>	<u>Total</u>
		<u>Info+MS</u>	<u>Info only</u>		
Total	23	82	50	6	161^a
Race-3	3	10	12	3	28
Race-2	3	41	11	1	56
Race-1	17	31	27	2	77

^a p=0.0001: calculated for advice given after physical examination.

ANR: Advised not to race

Overall in the 172 runners of the PRIMA-I group, 143 (83.1%) were given educational information. Of these 143 runners, 90 (62.9%) were advised to monitor symptoms, while 53 (37.1%) received information only. 23 runners were advised not to run, all after a physical examination. Further analysis of these 23 runners revealed that all had a systemic illness with ‘below-the-neck’ features. 12 had a LRTI, 6 a generalised URTI, 4 a systemic infective illness and 1 had suspected myo-pericarditis.

3.4.4. The incidence of not-starting the race (per 1000 runners) (‘Did not start’ rate: DNS rate)

3.4.4.1. Overall DNS rate

Of all the 53 976 runners who registered for the race in 2013 and 2014, 10 383 (192 per 1000 runners) did not start the race. The incidence (per 1000 runners) of not-starting the race (DNS rate) in all the groups is depicted in Table 3.7. In the CON group of 53 734 runners who did not attend the PRIMA facility, there were 10 329 non-starters (DNS rate = 192). Within the PRIMA group of 242 runners, 54 runners did not start (DNS rate = 223). There were 41 non-starters in the 172 runners in the PRIMA-I group (DNS rate = 238).

Table 3.7. The overall incidence (per 1000 runners) of not-starting the race (DNS rate)

	Starters		Non-starters		DNS rate (per 1000)	p-value
	N	%	N	%		
CON (n=53 734)	43 405	80.8	10 329	19.2	192	
PRIMA (n=242)	188	77.7	54	22.3	223	0.2561 ^a
PRIMA-I (n=172)	131	76.2	41	23.8	238	0.1510 ^a
PRIMA-N/I (n=70)	57	81.4	13	18.6	186	0.4704 ^b

^a Compared to CON

^b Compared to PRIMA-I

There was no significant difference in the DNS rate between the CON groups and any of the PRIMA groups.

3.4.4.2. The DNS rate in the PRIMA-I group based on the method of clinical assessment

The DNS rate in the PRIMA-I group, based on the method of clinical assessment, is depicted in Table 3.8. In the 172 runners in the PRIMA-I group, 11 were advised on the basis of medical history only (MHO). Only 1 runner did not start, indicating a DNS rate of 91. Of the 161 runners who were assessed by medical history and physical examination (MH+PE), there were 40 non-starters (DNS rate = 249).

There was no significant difference in the DNS rate between the groups. The number of non-starters in the MHO group was too small for statistical analysis (n=1).

Table 3.8. The DNS rate in the PRIMA-I group based on the method of clinical assessment (MHO and MH+PE)

	Starters		Non-starters		p-value	
	N	%	N	DNS rate		
CON (n=53 734)	43 405	80.8	10 329	192		
PRIMA-I (n=172)	131	76.2	41	238	0.1510 ^a	
	MHO (n=11)	10	90.9	1	91	
	MH+PE (n=161)	121	75.2	40	249	0.0878 ^a

^a Compared to CON

DNS rate: Runners who did not start (per 1000 runners)

3.4.4.3. The DNS rate in the PRIMA-I group based on advice given

The DNS rates in the PRIMA-I group based on advice given is depicted in Table 3.9.

Table 3.9. The DNS rate in the PRIMA-I group based on advice given

	Starters		DNS		p-value		
	N	%	N	DNS rate			
CON (n=53 734)	43 405	80.8	10 329	192			
PRIMA-I (n=172)	131	76.2	41	238	0.1510 ^a		
	Info (n=143)	116	81.1	27	189	0.9176 ^a	
		Info only (n=53)	47	88.7	6	113	0.1988 ^a
		Info+MS (n=90)	69	76.7	21	233	0.3926 ^a
	ANR (n=23)	10	43.5	13	565	< 0.0001 ^a	
	Other (n=6)	5	83.3	1	167	-	

^a Compared to CON

DNS rate: Runners who did not start (per 1000 runners)

There was no significant difference in the DNS rate between the main or sub-groups, compared to the CON group. However, in the group of 23 runners who were advised not to run (ANR), there were 13 non-starters (DNS rate = 565) and this is a significant increase in the DNS rate compared to the CON group. This indicates that 43.5% (the 10 runners who started) of this ANR subgroup were non-adherent to advice, while 56.5% were adherent.

3.4.4.4. The DNS rate in the PRIMA-I group based on the neck check

The DNS rates in the PRIMA-I group based on the neck check is depicted in Table 3.10. Of the

172 runners in the PRIMA-I group, 101 (58.7%) passed and 71 (41.3%) failed. The DNS rate was analysed overall, as well as depending on the day of PRIMA assessment. The DNS rate was compared between those runners seen within the day before the race (Race \leq -1), and those seen more than a day before the race (Race $>$ -1).

Table 3.10. The DNS rate in the PRIMA-I group based on the neck check

	Starters		DNS		p-value	
	N	%	N	DNS rate		
CON (n=53 734)	43 405	80.8	10 329	192		
Pass (n=101)	82	81.2	19	188	0.9167 ^a	
	Race $>$ -1 (n=49)	44	89.8	5	102	0.1555 ^a
	Race \leq -1 (n=52)	38	73.1	14	269	0.2178 ^a
Fail (n=71)	49	69.0	22	310	0.0182 ^a	
	Race $>$ -1(n=38)	31	81.6	7	184	0.9003 ^a
	Race \leq -1 (n=33)	18	54.5	15	455	$<$ 0.0001 ^a

^a Compared to CON

DNS rate: Runners who did not start (per 1000 runners)

Race $>$ -1: seen more than 1 day before the race

Race \leq -1: seen within 24 hours before the race

In runners who passed the neck check, there was no significant difference in the DNS rate compared to the CON group. However, in the 71 runners who failed the neck check, 22 did not start (DNS rate = 310) and this was significantly higher than the DNS rate in the CON group ($p=0.0182$). Furthermore, when analysing the DNS rate according to the day of assessment, a failed neck check on the day before the race resulted in a significantly higher DNS rate (455), compared to the CON group ($p<0.0001$).

3.4.5. The incidence of not-finishing the race (per 1000 runners) (‘Did not finish’ rate: DNF rate)

3.4.5.1. Overall DNF rate

In 2013 and 2014, 43 593 runners started the race; 42 920 (98.5%) finished the race while 673 runners did not finish (DNF rate = 15.4). The overall DNF rates are depicted in Table 3.11. In the CON group 43 405 started the race and 666 did not finish (DNF rate = 15.3), while 188 runners in the PRIMA group, started and 7 did not finish (DNF rate = 37.0)

Table 3.11. The DNF rate in all groups of starters

	Finishers		DNF		p-value
	N	%	N	DNF rate	
Control (n=43 405)	42 739	98.5	666	15.3	
PRIMA (n=188)	181	96.3	7	37.2	0.0329 ^a
PRIMA-I (n=131)	127	97.0	4	30.5	-
PRIMA-N/I (n=57)	54	94.7	3	52.6	-

^a Compared to CON

DNF rate: Runners who did not finish the race (per 1000 runners)

In the PRIMA group, 181 (96.3%) runners finished the race. However, the DNF rate (37) in the PRIMA group was significantly higher compared to the CON group (15.3) (p=0.0329). Although the DNF rates in both the PRIMA-I and PRIMA-N/I groups appear higher than that of the CON, statistical analysis was not performed because of the small sample sizes. Of the 7 runners who did not finish in the PRIMA group, all 7 were ultra-marathon runners, and 4 had symptoms of acute illness.

3.4.5.2. The DNF rate in the PRIMA-I group based on the method of clinical assessment

The DNF rates in the PRIMA-I group based on the method of clinical assessment are as follows. All 10 starters who had been assessed by MHO only, finished the race. Of the 121 starters who had been assessed by MH+PE, 4 did not finish (DNF rate = 33). Although there was an apparent higher DNF rate in the MH+PE group compared to the CON group, statistical analysis was not performed because of the small sample sizes.

3.4.5.3. The DNF rate in the PRIMA-I group based on advice given

The DNF rates in the PRIMA-I group based on advice given are as follows. All the runners who had been advised after the medical history only (n=10) finished the race. In the PRIMA-I group, 4 runners did not finish the race. Of these, 2 runners had been given information only, while 1 was also advised to monitor symptoms. The fourth had been advised not to run. Although the DNF rate is higher in the group of runners who had been advised after MH+PE (DNF rate = 33.1), compared to that of the CON group (DNF rate = 15.3), it was not statistically significant (p=0.0671).

3.4.5.4. The DNF rate in the PRIMA-I group based on the neck check

The DNF rates in the PRIMA-I group based on the neck check are as follows. In the PRIMA-I group 82 runners passed the neck check and started, only 1 did not finish (DNF rate = 12.2), but this was not statistically analysed because of the small sample size. In the PRIMA-I group 49 runners who started the race despite failing the neck check, 3 did not finish (DNF rate = 61.2). Two of the 3 runners were assessed on the day before the race. We note that the DNF rate in the runners who failed their neck check (61.2) appears to be higher than that of the CON, but statistical analysis could not be performed because of the small sample size.

3.4.6. The incidence of medical complications during or immediately after the race (per 1000 runners) (‘Medical complications’ rate: MC rate)

Of the 43 618 runners who started, 297 runners developed medical complications during or after the race, indicating a MC rate of 6.8 / 1000 starters. The MC rate in the CON group was 6.77 per 1000 starters, and there were no medical complications in the PRIMA-I group of runners who started the race (n=131).

3.5. Discussion

The main findings of this study relate to 1) clinical epidemiological data regarding acute illness in a cohort of runners with symptoms of acute illness in the 3 days before an endurance running event who were assessed at a medical facility, and 2) follow-up race participation data (not starting, not finishing and development of medical complications) in this cohort of runners.

3.5.1. Clinical epidemiology of acute illness in the pre-competition period

The main findings of this component of the study were that 1) more than 25% of runners who presented with symptoms of acute illness, had URT symptoms of sinus congestion, sore throat and runny nose, 2) lower RTS and systemic symptoms were common, with 38.4% of runners complaining of a cough (either productive or non-productive), 13.4% reporting fever and 12.8% complaining of fatigue, 3) in 93.6% of cases, a physical examination was conducted, in addition to a medical history, to make the diagnosis, 4) localised URTI comprised the majority of the diagnoses, (about 56% of ill runners), and 5) the most common individual diagnosis was URTI with generalised symptoms (22.7%).

We are not aware of any study where similar data have been reported. Therefore, there are no data for comparison but available evidence from studies conducted during events and tournament also report that URTI is the most common cause for acute illness in athletes. These data are based on tournament settings and self-reported symptoms only settings (15, 20-25). However, it is of interest that 9 of the 70 runners (12.9%) in the PRIMA-N/I cohort had RTS of non-infective origin. Some of these were diagnosed as allergic and others as wheezing after respiratory infection (WARI) or a post-infective cough. These data supports previous suggestions that a significant proportion of RTS, presumed to be infective in nature, may in fact have a different underlying aetiology (12, 13, 16, 18, 19).

3.5.2. Race participation data

The main findings related to participation data are that 1) 43.5% of runners who had been advised not to run, were non-adherent to this advice and started the race, 2) runners who passed the neck check were able to start and finish the race in a similar proportion to runners who did not present

with an acute illness (CON group), 3) runners who failed the neck check had a significantly higher rate of not starting compared to runners who did not present with an acute illness (CON group), 4) 54.5% of runners started despite a failed neck check, 5) runners who were assessed at the PRIMA facility had a higher incidence of not finishing the race, 6) there is some evidence to suggest that runners who failed the neck check had a greater risk of not finishing the race, but this finding was limited by small numbers, and 7) no runners in the PRIMA-I group, who started the race, reported medical complications at the race medical facilities.

The incidence of not-starting the race was used to determine adherence to advice given to the runners. Most runners appear to have adhered to advice given and there was a significantly greater DNS rate (per 1000 runners) in these runners compared to the CON group (565 vs. 192). However, it should also be noted that almost 45% of runners were non-adherent to this advice. An aspect of the educational information discussed with runners was the importance of monitoring symptoms. Advice was given with the intention of assisting runners make an informed decision about their fitness to compete. There may have been valid reasons for runners not to adhere to the advice given. There was a delay of up to 3 days before the race for some runners, and it is possible that their condition may have improved sufficiently to consider starting on race day. This delay may be responsible for some of those runners who started the race despite a failed 'neck check' or advice not to race. However, it should be noted that 73.9% (n=17) of the runners who were advised not to race, were examined within 24 hours of the race start, making this possible reason unlikely. Furthermore, running 'folk-lore' suggests that runners are notorious for ignoring medical advice. In fact, this may have had an impact on preventing runners from seeking help at the PRIMA facility, as several runners indicated that they did not want to be told they should not be running. Of interest was that when some of the ultra-marathon runners were advised against participating, they frequently expressed a wish to participate in the half-marathon instead, perceiving it as less 'risky'. This is in accordance with data describing drop-outs in the Aberdeen marathon in 1984, where a third of the 'drop-out' respondents indicated they would have entered a half-marathon if given the option (70).

It is interesting to note that the DNS rate in the entire race population was 192 per 1000. This is a much lower rate than has previously been recorded in the literature. There are not many data, but information from three studies indicate that pre-race 'drop-out rates' in marathon races vary between 30-55%, mainly due to injury, illness and motivational reasons (70-72). Entries to the Two Oceans Marathon races are highly sought after, especially the half-marathon, which is

usually oversubscribed (85) and this may explain the lower ‘drop-out’ rate in this race compared with the data reported from other races.

In this study, 56.5% runners who were advised not to run apparently took this advice and did not start. We acknowledge that their illness may not have been the only reason for not starting. In terms of general advice given to runners, there was a DNS rate of 56 in those runners who were given information only, 233 in those who were advised to monitor symptoms and the aforementioned 565 in those advised not to run. This difference in the DNS rate may indicate the severity of their illness and that those runners who were advised not to run were more ill than those advised to monitor symptoms, or those who received information only. We are not aware of any data in the published literature that explore the concept of adherence to advice against participating, when athletes have evidence of acute illness.

The neck check is a clinical tool that SEM physicians use to advise athletes regarding safety to participate if they suffer from a recent or a current acute illness. To our knowledge, there are no clinical studies that explored the application of the neck check in a population of athletes with acute illness in the pre-competition period. Therefore, we cannot compare our results to any published data. In our study, runners with localised or minimal pre-race illness who passed the neck check *i.e.* had ‘above-the-neck’ symptoms, had the same chance of starting the race as runners in our control group. Furthermore, of those runners who started after passing their neck check, 98.8% finished the race and did not have any medical complications. Therefore, advice to allow participation in runners with ‘above-the-neck’ symptoms appears to be safe and have no impact on the ability to complete the race. These data are, to our knowledge, the first clinical data from a prospective study to indicate that the ‘neck check’ is a useful and valid clinical tool to advise athletes with acute illness on RTP. However, we do encourage further research in this area, particularly with more specific diagnoses and larger sample sizes, and more accurate measures of performance (*e.g.* split and finishing times compared to previous or personal best running times).

We also note that 90% of the starters, who had been advised not to run, finished the race without medical complications. The diagnoses in this group of runners (advised not to run) were all systemic in nature. Our study sample size is too small to imply that running with such conditions is safe, but it does indicate that further clinical studies with larger numbers are important, particularly as there are documented risks of exercising whilst suffering from a systemic infection (Chapter 2).

A failed neck check was associated with a significantly higher incidence of non-starters; this increase was even more significant when runners were seen within 24 hours of the race start. As the time between examination and race decreased, there was an increasing proportion of non-starters in both groups – passed and failed neck check. The highest proportion of neck check failures was seen on Race Day -1 (*i.e.* the day before the race), although this coincided with almost half (49.4%) of the PRIMA-I cohort being seen on that day. In these runners, there was a minimal time delay between advice and the race, allowing little time for improvement of clinical condition. Despite this, more than 50% (54.5%) failed to adhere to the advice that would have cautioned against starting with ‘below-the-neck’ symptoms.

The DNF rate in the runners who failed a neck check (61 per 1000) appears to be higher than the CON group (16), but this finding should be interpreted with caution due to the small numbers of participants in these groups. Further studies with larger sample sizes are needed.

There were no medical complications recorded for the PRIMA-I cohort, compared to the overall race incidence of medical complications of 6.81 per 1000 starters. The overall incidence of medical complications for this race has previously been reported as 8.27 per 1000 over a 4 year period (84). In evaluating the role of a pre-race registration medical facility it is perhaps expected that the ‘acutely ill runners’ would have a higher incidence of medical complications. However, this was not the case in this study. We suggest that the advice provided to all athletes during PRIMA consultations may have reduced the risk of short-term medical complications in runners with pre-race symptoms of acute illness. However, this requires further study with a larger sample size.

In the PRIMA-N/I (non-infection) cohort, the PRIMA facility played a role in the prevention of potential medical complications. In this group, 2 runners were referred for suspected DVTs, while a third runner was found to have runs of SVT of 240 beats / min in the days prior to the race. A fourth runner had significant hypertension with a BP of 194/114 mmHg. These runners were advised against running due to the risk of cardiac or pulmonary complications and were referred for further urgent medical care.

3.5.3. Strengths and limitations of the study

This study has a number of strengths. Firstly, as far as we are aware, this study is the first to document the clinical epidemiology of illness in athletes in the 3 days before an event, and then document follow-up race participation data (not starting, not finishing and development of medical complications) in this cohort of runners in the form of a prospective study. Secondly, an accurate clinical diagnosis was made by qualified medical staff in the cases of ill runners. This is in contrast to previous studies that relied on self-reported data only. Thirdly, we were able to compare our data to a large control group of runners.

There are however also some limitations of this study. Firstly, the cohort of runners in the PRIMA group was of a self-selected nature. Therefore the prevalence of acute illness in the entire race population is not known. It is likely that some runners in the control group also suffered from symptoms of acute illness but did not report to the PRIMA facility. This has implications for the DNS, DNF and MC rates, which may be affected by runners in the CON group that also suffered from acute illness at the time of the race. Therefore, if anything, the DNS, DNF and MC rates of runners with no illness are lower than that reported for the CON group in this study. Secondly, we did not identify the reasons for not starting or finishing a race in runners. Therefore, we cannot assume that not-starting or not-finishing was as a result of acute illness or advice given. This should be determined in future studies of this nature. Finally, we acknowledge that the sample sizes were very small in some of our sub-groups, and we could therefore not perform adequate statistical analyses of these sub-groups. Future studies with larger participant numbers will address these limitations.

3.5.4. Summary and conclusion

In conclusion, this study is the first to investigate a pre-race population of runners with acute illness that were diagnosed after a clinical assessment. In this cohort of 172 ultra- and half marathon runners, the majority of acute illness was localised to the upper respiratory tract, but a significant number of runners had an URTI with generalised symptoms, as well as LRTI. These runners were given advice on participation guidelines, based on the neck check. More than half of the runners, who were advised not to run, appear to have taken heed of this advice. Of concern were the 43.5% who were non-adherent to advice. The vast majority of race starters finished safely, supporting the first tenet of the neck check *i.e.* exercising with ‘above-the-neck’ (localised

URT symptoms) is safe. The lack of medical complications in the small number of those runners who exercised with 'below-the-neck' / systemic symptoms, should not be used to imply safety and further studies with larger sample sizes are needed. However, this study therefore provides the first clinical data to support the application and safety of the neck check as a participation guideline in athletes with acute illness in the pre-competition period. However, further studies should also investigate the effects of different types of infections as well as the sub-acute health complications in the days or weeks after participation.

Chapter 4

Summary and conclusion

4.1. Summary of main findings

The focus of this dissertation was to gain an understanding of current participation guidelines with respect to acute illness in athletes. In Chapter 2, the evidence behind the current guidelines, which are based on the neck check, a clinical tool commonly used by SEM physicians, was reviewed. This review indicated that there have been no clinical studies that investigated the use of the neck check as a participation guideline in such athletes. Furthermore, there is no indication in the literature as to whether athletes adhere to the medical advice they are given. With these questions in mind, the original research component was undertaken.

From an epidemiological perspective, the review indicated that the upper respiratory tract is the most common source of symptoms of illness in athletes. However, the literature in this regard is based on self-reported symptomatology as opposed to confirmation of the diagnosis following clinical examination or special investigations. There is good evidence that not all URTS are infective in nature, and they may be related to allergy or inflammation of unknown aetiology, induced by physiological stress. The value of physical examination in addition to a medical history only, was confirmed. The review furthermore showed that there is a 'Participation risk', pertaining to acute illness in athletes. There are potential medical complications of exercising whilst ill and these include the potential risks of sudden cardiac death (SCD) when exercising with sub-clinical myocarditis, splenic rupture in patients with infectious mononucleosis (IM), electrolyte disturbance with gastroenteritis, reductions in pulmonary function with lower respiratory tract infection (LRTI) and influenza, as well as acute renal failure and exertional heatstroke. There are also few clinical data and little scientific reports on the effects of acute illness on impaired exercise performance and non-participation as a result of acute illness. The history and the evidence base for the validity of the neck check, in terms of safety of exercising with localised URTS, as well as potential risks of exercising with lower respiratory or systemic illness were reviewed. It was concluded that there are very few clinical and research data supporting the use of the 'neck check' to advise athletes on return to play (RTP) following an acute illness.

Therefore, the research study in this dissertation is, according to our knowledge, the first study that examined the epidemiology of illness in a pre-race cohort of runners, and then followed these runners until after the race to assess adherence to advice, race starting and finishing as well as medical complications. In this cohort of 172 runners, localised URTI constituted the majority of clinical diagnoses, of which sinusitis, pharyngitis and non-infective rhinitis were the most common diagnoses. These findings support the evidence suggesting that URTS are the most common cause of infection in athletes. This is important as we know that there is a significant overlap between the symptoms of these conditions, especially sinusitis and rhinitis, and symptoms of allergy. However, the single most common diagnosis in our study was that of an URTI with generalised symptoms. A novel finding in our study is that our data support the short-term safety of exercising with symptoms of localised URTI *i.e.* a ‘passed’ neck check, as 96.95% of the starters in the study cohort finished without requiring medical assistance during or after the race.

However, we do report that a failed neck check increased the incidence of not starting the race, as well as increasing the incidence of not finishing in those who started. Further studies with larger sample sizes are required to investigate the race participation outcomes and medical complication rate in those runners with a failed neck check, or suffering from ‘below-the-neck’ or systemic illness. Although the results of our study suggest that it is safe to use the ‘neck check’, further studies with larger sample sizes are required to confirm this finding. We do suggest that pre-race medical facilities that assist athletes with symptoms of acute illness have the potential to reduce the risk of medical complications in a large endurance event, and this also needs further exploration in studies with larger sample sizes. Finally we do note, with some concern, that there was a high level of non-adherence to advice given against participation (43.5%) in a pre-race registration medical facility. The reasons for this high level of non-adherence also need to be explored in future studies.

4.2. Clinical implications of findings

The current participation guidelines for athletes with acute illness were summarised in the concluding section of Chapter 2. In the evaluation of an athlete with symptoms suggesting acute illness in the pre-competition period, the following are additional suggestions to these guidelines for the SEM physician, based on the findings of this dissertation:

1. A pre-race registration medical facility should be considered in all large endurance events with a view to reducing potential medical complications.
2. The medical assessment at such a facility should include both a medical history and physical examination by a SEM physician.
3. Aetiologies other than infection for upper respiratory tract symptoms should be considered: the medical history should specifically enquire about allergies.
4. Physical examination is necessary to rule out diagnoses such as streptococcal pharyngitis, infectious mononucleosis and possible myocarditis. Body temperature, resting heart rate and respiratory rate should be noted. Special investigations may be helpful, specifically rapid assays for *GABHS*, serum inflammatory and cardiac markers, and a resting ECG.
5. The neck check appears to be a safe clinical tool to direct participation advice, especially in those runners with ‘above-the-neck’ illness.
6. Education of athletes during encounters at such facilities is essential for runners to make an informed decision about their individual participation risk on the day of the race.

4.3. Suggestions for further research

We suggest that further research be conducted in this area, particularly an extension of this study with a larger sample size. The following additional areas for research should be considered in a larger cohort:

1. Determining risk factors for infection:
 - Training load is described as a risk factor for infection: training history could be analysed in this cohort. It is anticipated that there may be proportionally more illness in the ultra-marathon sub-population.
 - History of allergy increases the risk of symptoms of URTI – medical history could be examined.
 - Recent or current symptoms of infection and exploring if these are a risk factor for developing medical complications during or after an endurance event.
 - Exploring other risk factors for acute illness including presence of other chronic diseases in runners, use of medication and supplements, age of runners, and the possible effects of travelling.
2. Exploring the possible effects of illness on performance by examining finishing and split times, and also comparing to previous race times or personal best times.

3. Determining the effect of a failed neck check on exercise performance and potential medical complications.
4. Exploring the safety and effects on performance when exercising with WARI (wheezing following respiratory tract infections), which is a known complication that appears to affect certain sub-groups of athletes. Such data are lacking. Although some of the runners in the PRIMA group were noted to have post-infectious respiratory tract symptoms, there were too few numbers for analysis.
5. Determining if there are differences in race participation and safety with regard to specific diagnoses *i.e.* specific localised URT infection or systemic illnesses.
6. Conducting follow-up studies to ascertain the following:
 - Reasons for not-starting the race.
 - Reasons for non-adherence to advice if advised against participation.
 - Medical complications, which may have arisen in the days or weeks following the race.
7. Exploring, through laboratory-based research, the development of a simple novel biomarker which could distinguish between viral and bacterial infection, as well as non-specific inflammation.

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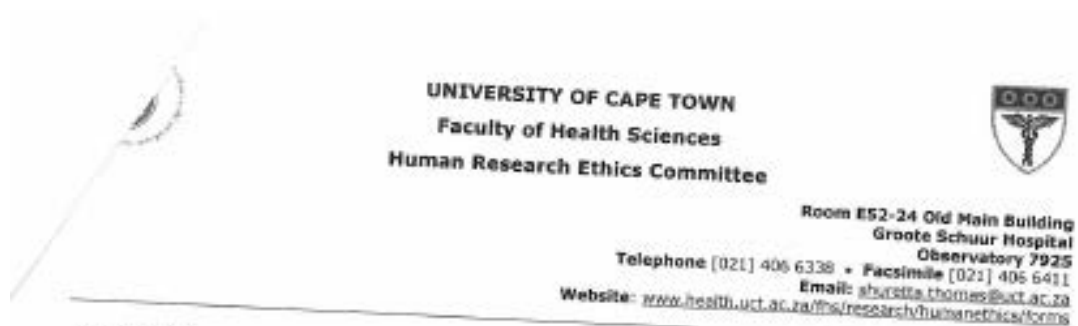
Appendices

Appendix A: Ethics approval: Page 1

RESEARCH ETHICS COMMITTEE	
UNIVERSITY OF CAPE TOWN	704 - 07 - 0 1
HEALTH SCIENCES FACULTY	FACULTY OF HEALTH SCIENCES
UNIVERSITY OF CAPE TOWN	Human Research Ethics Committee
Form FHS007: Amendment – study staff	
HREC office use only (FWA00001637; IRB00001938)	
<input type="checkbox"/> Approved	
This serves as notification that all changes to the study staff and documentation described below are approved.	
Chairperson of the HREC signature	Date 11/7/2014
Principal Investigator to complete the following:	
1. Protocol information	
Date	12 May 2014
HREC REF Number	REC 441/2012
Protocol title	MEDICAL CONSEQUENCES IN ENDURANCE SPORTS: TWO OCEANS MARATHON LONGITUDINAL STUDY: 2013-2015
Protocol number (if applicable)	N/A
Principal Investigator	Prof Martin Schwellnus
Department / Office Internal Mail Address	Human Biology
1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2. Items for approval	
Please list on the page below all staff changes and additional documentation such as CVs and revised consent forms which need approval. This information must correspond to all 'yes' answers below. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.	
3. List of documentation (eg: CVs, Declarations & GCP Certificates)	
Dr. Leigh Gordon is added to the co-investigator list. She is an MPhil Sport and Exercise Medicine student and will explore a component of the data that have been collected during this study. In particular, she will investigate the following: 1) the epidemiology of symptoms of an acute illness in runners in the week before the race, 2) the clinical findings in runners who reported with symptoms of acute illness, 3) the adherence to the advice given to runners with symptoms, and 4) the consequences (race participation) of runners with symptoms.	
4. Staff changes (tick ✓)	
Are new personnel being added to this research?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Are current personnel being removed from this research?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
16 April 2012	Page 1 of 2

UNIVERSITY OF CAPE TOWN	
FACULTY OF HEALTH SCIENCES	
Human Research Ethics Committee	
Is the principal investigator for this research being changed?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If yes, please attach revised conflict of interest and PI declaration statements. (Refer: sections 7 and 8.4 in the New Protocol Application Form)	
Do the consent and assent forms need modification to reflect these staff changes?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If yes, please attach copies of the revised forms, with all changes highlighted or tracked.	
5. Signature	
My signature certifies that I will maintain the anonymity and/or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.	
Signature of PI	Date 12 May 2014
Signature of Supervisor (if PI is a student)	

Ethics approval: Page 2



01 July 2014

HREC REF: 441/2012

Prof M Schwellnus
Sports Science Institute
Human Biology

Dear Prof Schwellnus

**PROJECT TITLE: MEDICAL CONSEQUENCES IN ENDURANCE SPORTS TWO OCEANS
MARATHON LONGITUDINAL STUDY: 2013-2015**

The HREC confirms that the MPhil Sport & Exercise Medicine student, Dr Leigh Gordon, is part of the above-mentioned study and his approval is covered under this HREC reference number.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Appendix B: Electronic questionnaire completed in the Health Village for PRIMA Consultation

1. Date [free text, compulsory]

2. Runner Identification

Surname [free text, compulsory]

First name [free text, compulsory]

Sex [drop down box, single select, compulsory]

Male

Female

Age [free text, compulsory]

Cell number [free text]

Race number [free text, compulsory]

Race [drop down box, single select, compulsory]

21 km

56 km

Short trail run

Long trail run

Fun run

Other: [free text]

3. Runner triaged by [free text compulsory]

4. What is the primary presenting symptom? [drop down box, single select, compulsory]

Abdominal cramps

Abdominal pain

Arthralgia

Chest pain

Cough – non-productive

Cough - productive

Diarrhoea

Dysuria

Earache

Fatigue

Fever

General body aches

Haematuria

Headaches

Muscle cramps

Myalgia

Nausea

Nausea and vomiting

Palpitations

Runny nose

Shortness of breath

Sinus congestion

Sore throat

Tight chest

Other: [free text box]

5. What are the secondary presenting symptoms? (You may select more than one.)
[drop down box, multiple select]

Abdominal cramps

Abdominal pain

Arthralgia

Chest pain

Cough – non-productive

Cough - productive

Diarrhoea

Dysuria

Earache

Fatigue

Fever

General body aches

Haematuria

Headaches

Muscle cramps

Myalgia

Nausea

Nausea and vomiting

Palpitations

Runny nose

Shortness of breath

Sinus congestion

Sore throat

Tight chest

Other: [free text box]

6a. Is a physical examination indicated? [drop down box, single select, compulsory]

Yes

No

6b. Does the runner give consent to a physical examination? [drop down box, single select, compulsory]

Yes

No

7. [If NO was clicked in question 6a or 6b]

What advice was given? (you may select more than one) [drop down box, multiple select, compulsory]

Advised not to race
 Advised to monitor symptoms and decide on race day
 Educational information given and discussed – Acute infections
 Educational information given and discussed – Gastroenteritis
 Educational information given and discussed – Respiratory tract infections
 Medication prescribed: [free text box]
 Referral to Dr/hospital – non-urgent
 Referral to Dr/hospital – urgent
 Other: [free text]

8. [If YES was clicked in question 6a and 6b]
 Physical examination (vital signs)

Resting heart rate [free text box]
 Resting systolic pressure [free text box]
 Resting diastolic pressure [free text box]
 Tympanic temperature [free text box]

9. Runner examined by: [free text compulsory]

10. Physical examination (general) (you may select more than one)
 [drop down box, multiple select, compulsory]

None
 Pale
 Jaundice
 Cervical lymphadenopathy – right neck
 Cervical lymphadenopathy – left neck
 Peripheral oedema
 Clammy/sweaty
 Abnormal skin turgor
 Dry mucous membranes
 Other [free text]

11. Physical examination (ENT) [drop down box, single select, compulsory]

Not indicated
 Normal
 Abnormal

If abnormal, please indicate findings (you may select more than one): [drop down box, multiple select]

Nasal discharge – clear
 Nasal discharge – purulent
 Nasal discharge – bloody
 Otorrhoea
 Pharyngitis – mild erythema

Pharyngitis – with exudate
 Pharyngitis – with other signs
 Post-nasal drip
 Sinus tenderness – maxillary
 Sinus tenderness – frontal
 Sinus tenderness – other
 Tonsillitis
 Tympanic membrane erythema
 Other: [free text]

12. Physical examination (respiratory) [drop down box, single select, compulsory]

Not indicated
 Normal (no evidence of crepitation, effusion, rhonchi, rub, wheezing etc.)
 Abnormal

If abnormal, please indicate findings (you may select more than one):[drop down box, multiple select]

Crepitations
 Effusion
 Rhonchi
 Rub
 Wheeze
 Other: [free text box]

13. Physical examination (abdominal) [drop down box, single select, compulsory]

Not indicated
 Normal
 Abnormal

If abnormal, please indicate findings (you may select more than one):[drop down box, multiple select]

Tender – no peritonitis
 Tender – suspicious of peritonitis
 Other: [free text]

14. Physical examination (cardiovascular) [drop down box, single select, compulsory]

Not indicated
 Normal
 Abnormal: [free text]

15. Physical examination (neurological) [drop down box, single select, compulsory]

Not indicated
 Normal
 Abnormal: [free text]

16. Physical examination (musculoskeletal) [drop down box, single select, compulsory]

Not indicated
 Normal
 Abnormal [free text]

17. Physical examination (other) : [free text]

18. What is the main working diagnosis/clinical problem? [drop down box, single select, compulsory]

Angina- stable
 Angina – unstable
 Arrhythmia – ventricular
 Arrhythmia – supraventricular
 Arrhythmia – other
 Bronchospasm
 Chest pain – unspecified
 Gastroenteritis – mainly diarrhoea
 Gastroenteritis – mainly vomiting
 Gastrointestinal disease – other
 Laryngitis – localised
 Lower respiratory tract infection
 Myopericarditis (suspected)
 Otitis media
 Pharyngitis – localised
 Rhinitis – localised – infected
 Rhinitis – localised – non-infected
 Sinusitis – localised
 Upper respiratory tract infection – generalised
 UTI (suspected)
 Other: [free text]

19. Additional clinical problems/diagnoses? (you may select more than one) [drop down box, multiple select]

Angina- stable
 Angina – unstable
 Arrhythmia – ventricular
 Arrhythmia – supraventricular
 Arrhythmia – other
 Bronchospasm
 Chest pain – unspecified
 Gastroenteritis – mainly diarrhoea
 Gastroenteritis – mainly vomiting
 Gastrointestinal disease – other
 Laryngitis – localised
 Lower respiratory tract infection
 Myopericarditis (suspected)

Otitis media
Pharyngitis – localised
Rhinitis – localised – infected
Rhinitis – localised – non-infected
Sinusitis – localised
Upper respiratory tract infection – generalised
UTI (suspected)
Other: [free text]

20. What advice was given? (you may select more than one) [drop down box,
multiple select, compulsory]

Advised not to race
Advised to monitor symptoms and decide on race day
Educational information given and discussed – Acute infections
Educational information given and discussed – Gastroenteritis
Educational information given and discussed – Respiratory tract infections
Medication prescribed: [free text box]
Referral to Dr/hospital – non-urgent
Referral to Dr/hospital – urgent
Other: [free text]

Appendix C: Three informational leaflets given to athletes at a PRIMA consultation

1. Guidelines: Running and acute infections

Guidelines Running and acute infections

Runners that are training very hard may be more susceptible to acute (new onset) infections. Therefore, at the peak of your preparation for the race you may have symptoms of an acute infection. These vary according to the body system that is affected but the common general symptoms of an infection are: fever, headache, general body aches and pain, and excessive tiredness (malaise). Depending of the body part that is affected, other symptoms may also be present.

If you have symptoms of any acute infection (including bladder infections, skin infections etc.), especially in the week before the race, we strongly urge you to seek a medical opinion from a qualified medical doctor.

Taking part in exercise while having an infection can be very detrimental to your health and can cause serious complications. Some of the infective agents (viruses or bacteria) can, for example, affect the heart muscle (known as myocarditis), resulting in heart muscle damage and even sudden cardiac death. There are very strict guidelines to assist you in preventing complications during running when you have symptoms of an infection.

Please take note that if you have any of the following symptoms of an infection, it is recommended that you do **NOT** take part in exercise:

- Fever
- General muscle pains
- General joint pains
- Chest pain
- Increase in your resting pulse rate
- Shortness of breath (more than usual)
- General tiredness (fatigue) that is more than usual

If you have any of these symptoms, or other symptoms of an infection, we suggest that you do NOT train or race, and consult your doctor for further advice and treatment.

At the Two Oceans registration (Expo) there will be medical staff to assist you if you do have any of these symptoms. The staff will be able to offer advice on running and infections.

Old Mutual Two Oceans Marathon Medical Team

Prof Martin Schwellnus, Prof Wayne Derman, Dr Karen Schwabe, Dr Wayne Smith

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2. Guidelines: Running and respiratory tract infections

Guidelines Running and respiratory tract infections ("flu" and "common cold")

Respiratory tract infections are the most common infections of affecting athletes and are caused by viruses (mostly), bacteria or other organisms. However, symptoms of respiratory tract infections may also be caused by a non-infectious cause such as an allergy. These infections mainly affect the nose, sinuses or throat area and are then known as upper respiratory tract infections.

Symptoms of an upper respiratory tract infection are blocked nose, runny nose, sore throat, and painful sinuses. These infections do not usually result in symptoms affecting the whole body (fever, muscle pain, joint pain, general tiredness).

If the infection spreads to the airways and lungs this is known as a lower respiratory tract infection. Typical symptoms of a lower respiratory tract infection are cough, chest pain, and shortness of breath. Usually, but not always, these infections are associated with symptoms affecting the whole body (fever, muscle pain, joint pain, general tiredness).

Running and respiratory tract infections

Taking part in exercise while having an infection can be very detrimental to your health and can cause serious complications. Some of the viruses can affect the heart muscle (known as myocarditis), resulting in heart muscle damage and even sudden cardiac death. Please remember that other infections, such as measles and chickenpox affect the respiratory tract and your whole body. They are contagious and it is recommended that you do not exercise when you suffer from these illnesses.

There are very strict guidelines to assist you in preventing complications during running when you have symptoms of a respiratory tract infection.

Please take note that if you have any of the following symptoms of respiratory tract infections, it is recommended that you do **NOT** take part in exercise:

- Fever
- General muscle pains
- General joint pains
- Chest pain
- Increase in your resting pulse rate
- Shortness of breath (more than usual)
- General tiredness (fatigue) that is more than usual
- Severe sore throat
- Swollen and painful lymph nodes in your neck

If you have any of these symptoms we suggest that you do NOT train or race, and consult your doctor for further advice and treatment.

In some mild cases where your symptoms are only in the upper respiratory tract (no generalized body symptoms) your doctor may allow some form of low-moderate intensity exercise. If you do decide to race, we suggest you see how you feel after 10 minutes or so. If you feel unwell we suggest that you stop running.

At the Two Oceans registration (Expo) there will be medical staff to assist you if you do have any of these symptoms. The staff will be able to offer advice on running and respiratory tract infections.

When can you resume running after a respiratory tract infection?

It is suggested that you can return to running after a respiratory tract infection only when all your symptoms have disappeared and you feel well again. If you are not sure, please have an evaluation by a qualified medical doctor.

Old Mutual Two Oceans Marathon Medical Team

Prof Martin Schwellnus, Prof Wayne Derman, Dr Karen Schwabe, Dr Wayne Smith

3. Guidelines: Running and gastro-enteritis

Guidelines Running and gastro-enteritis (gastro-intestinal infections)

Gastro-enteritis (including gastro-intestinal infections), is very common in athletes, particularly when travelling. The causes of gastro-enteritis can be as a result of an infection or a toxin (“food poisoning”). The typical symptoms of gastro-enteritis are nausea, vomiting, diarrhoea and abdominal cramping (pain).

Acute gastro-enteritis can have detrimental effects on your ability to run, largely as a result of dehydration and electrolyte disturbances. Electrolytes are the salts in your blood such as sodium and potassium. Symptoms affecting your whole body such as fever, muscle pain, joint pain, and general tiredness may also occur.

There are very strict guidelines to assist you in preventing complications during running when you have symptoms of gastro-enteritis. Running with gastro-enteritis may aggravate the effects of dehydration and electrolyte abnormalities, which can cause confusion or other brain disturbances, or trigger abnormal heart rhythms and possibly even sudden cardiac death.

Please take note that if you have any of the following symptoms of gastro-enteritis, it is recommended that you do **NOT** take part in exercise:

- Fever
- General muscle pains
- General joint pains
- Dehydration (dizziness when standing, decreased urine volume and concentrated urine, thirst, dry mouth and decreased saliva production)
- On-going nausea and vomiting
- On-going abdominal cramps
- Increase in your resting pulse rate
- General tiredness (fatigue) that is more than usual

If you have any of these symptoms we suggest that you do NOT train or race, and consult your doctor for further advice and treatment.

At the Two Oceans registration (Expo) there will be medical staff to assist you if you do have any of these symptoms. The staff will be able to offer advice on running and gastro-enteritis.

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