Medical consequences following endurance sport

Acute pre-race illness – the effect of a screening and educational intervention program on race participation, inability to finish a race and medical complications during a race

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Declaration

I, Anri van Tonder, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

Signed by candidate

(Signature)

February 2015

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(Date)

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List of abbreviations

ATP (Adenosine triphosphate)

BMI (Body mass index)

CHO (Carbohydrate)

CK (Creatine kinase)

CK-MB (Creatine kinase isozyme MB)

CRP (C-reactive protein)

DNF (Did-not-finish)

DNS (Did-not-start)

ECG (Electrocardiogram)

FBC (Full blood count)

HCM (Hypertrophic cardiomyopathy)

IM (Infectious mononucleosis)

MC (Medical complication)

METS (Metabolic equivalents)

NK (Natural killer)

NKCA (Natural killer cell activity)

PCR (polymerase chain reaction)

PVFS (Post-viral fatigue syndrome)

RCT (Randomized control trial)

RTP (Return to play)

sIgA (Saliva secretory immunoglobulin A)

URT (upper respiratory tract)

VO_2Max (Maximal oxygen consumption)

TNF-α (Tumor necrosis factor α)

WCC (white cell count)

Abstract

Background

It is well established that athletes, including long distance runners, can be more prone to acute upper respiratory tract (URT) illnesses during periods of intense and prolonged training. Therefore, a sport and exercise medicine physician frequently advise on the athlete's eligibility for participation in a sport event or exercise session. To date, a clinical tool called the "neck check" was utilized as a guideline for such advice. There are however very little evidence available in the literature 1) to validate this guideline, 2) predict how many runners will have symptoms of an acute illness one week prior to an endurance race, 3) predict how many runners will "fail" the "neck check" in the 7-day period before a race and would be advised not to participate, 4) what the influence of educational information and guidelines on the acutely ill athlete's decision on participation in the race will be, and 5) how many runners, with an acute pre-race illness who choose to start the race, do not finish the race or develop medical complications during the race.

Objective

The main objectives of this dissertation was: 1) to review the available evidence with respect to the period prevalence of pre-race upper respiratory tract infections (the week before a distance running event) in distance runners, the relationship between exercise and infections, and the possible health consequences of participating in sport whilst suffering from an acute infective illness; 2) to document the period prevalence of runners with an acute illness in the 7-day period prior to an endurance race; 3) to determine the period prevalence of runners who "fail" the "neck check", and would be advised not to participate in the race, 4) to determine the incidence of runners with an acute illness, and who received educational information and guidelines, and who then not start the race, 5) to determine the incidence of runners with an acute illness

who chose to start the race, but do not finish the race, and 6) to determine the incidence of runners with an acute illness who chose to start the race, but develop medical complications during the race.

Methods

Phase 1: Review of the literature utilizing evidence based principles
Electronic databases were utilised to source literature relating to the epidemiology of acute illness in athletes, the relationship between exercise and the immune system, risk factors for illness, the effect illness has on exercise performance and various systems of the body, return-to-play guidelines for the ill athlete, potential medical complications when exercising with an acute illness, and possible preventative strategies to avoid becoming ill.

Phase 2: Research study
In a prospective cohort study, 7035 runners were recruited (5954 by email 5 days prior to the race, and 1085 by interviews held in the 3-day period prior to the race during registration at the expo). All the participants completed a pre-race acute illness questionnaire in which they reported if they experienced one or more symptoms of an acute illness in the 7-day period prior to the race. All runners who indicated that they experienced any symptoms (N=1338) received an educational information leaflet (either via email or as a hand-out at the expo). The leaflets contained general information about acute illness, information about the risk to exercise with the illness, and specific guidelines on when not to participate while certain symptoms are present.

Based on the response to the pre-race acute illness questionnaire, the 7035 runners were firstly categorized into an asymptomatic control group (n=5697), and a symptomatic group (including all the runners with any symptoms of an infection) (n=1338). Runners in the symptomatic group were further divided into sub-groups as follows: systemic symptoms group (n=530), respiratory symptoms

group (n=896), gastrointestinal symptoms group (n=249) and runners who failed the “neck check” (n=878). All runners (N=7035) were then followed on race day and information about each runner was obtained from a database of the race organizers. Data were obtained on the number of runners who did not start the race, and runners who started the race but did not finish the race. Data were also obtained from the medical stations on route and the medical tent at the finish line. All runners who were treated at a medical facility were considered to have a medical complication.

The following outcome variables were then compared between the control group and the symptomatic group and sub-groups: 1) The period prevalence (%) of runners with symptoms of an acute illness in the 7-days prior to an endurance race, 2) the did-not-start (DNS) rate (% runners) in runners in different groups, 3) the did-not-finish (DNF) rate (% runners) in runners in different groups, and 4) the medical complication (MC) rate (% runners) in runners in different groups.

Results

Phase 1: Review

The review showed that there are very little data on the period prevalence of an acute illness in the few weeks prior to an endurance running race. It is however well established that endurance athletes (including distance runners) are at an increased risk to develop an upper respiratory tract (URT) illness during periods of high volume training (high intensity, long duration/ distance or high frequency) and the relationship between the “dose of exercise” and the risk to develop an URT illness follows a “J” shaped curve. In most studies there was reliance on self-reported symptoms using questionnaires and as such, URT illness were never diagnosed as being infective. Other causes for URT illness symptoms, such as allergies or asthma, should thus be investigated.

Specific risk factors for athletes for the development of an URT illness were identified and the influences that exercise has on various parameters in the immune system were reviewed. An acute illness can negatively affect an athlete's exercise performance as well as have effects on various systems in the body. The systems most affected are the neurological system, cardiovascular system, musculoskeletal system, metabolic system and thermoregulation and the influences on these systems are discussed. Exercising with an acute illness is not without risk and the potential medical complications, including myocarditis and rhabdomyolysis, are reviewed. Possible strategies to prevent acute infections in distance runners are reviewed.

Several guidelines in relation to the return-to-play guidelines for athletes with an acute illness were identified. The most common clinical tool that is used by clinicians to advise athletes on return-to-play (RTP) following acute illness is the "neck check". There are however no published data validating the use of the "neck check" as a RTP guideline.

Phase 2: Research study

In the cohort of 7035 runners, 1138 runners (19.02%) experienced symptoms of an acute illness in the 7-day period prior to the race. The most common symptom experienced by the runners was a sore throat (34.5%), followed by a runny nose (29.9%), general tiredness (27.8%), a blocked nose (23.3%) and headaches (22.6%). When these symptoms experienced by the runners during the week prior to the race were grouped into clusters of symptoms, 530 runners (7.5%) experienced acute systemic symptoms, 896 runners (12.7%) experienced acute respiratory symptoms and 249 runners (3.5%) experienced acute gastrointestinal symptoms. In addition, 6157 runners (87.5%) passed the "neck check", while 878 runners (12.5%) failed the check.

The did-not-start (DNS) rate for the symptomatic group was 10.8%, which was significantly higher than the DNS rate for the control group (asymptomatic

runners)(6.2%)($p<0.0001$). In the sub-groups of symptomatic runners, the DNS rate for the runners with systemic symptoms was highest (14.7%) and this was significantly higher than the control group ($p<0.0001$). Runners who experienced gastrointestinal symptoms also had a high DNS rate of 12.1% ($p=0.0003$ vs. the control group), while runners who experienced respiratory symptoms had a DNS rate of 11.7% ($p<0.0001$ vs. the control group). Similarly, the DNS rate for the runners who failed the “neck check” was 12.2% ($p<0.0001$ vs. the control group).

The DNF rate for the control group was 1.8%, which was similar to that of the symptomatic group (2.2%) ($p=0.3778$). Runners who experienced systemic symptoms in the 7 days prior to the race had the highest DNF rate (2.7%) ($p=0.1954$ vs. control), followed by the runners who experienced gastrointestinal symptoms during the 7 days prior to the race (2.3%) ($p=0.16$ vs. control) and runners who experienced respiratory symptoms (1.8%) ($p=0.9571$ vs. control). Runners in the failed “neck check” group had a DNF rate of 2.2% ($p=0.4319$ vs. control). There was also no statistically significant difference in the medical complication rates between the symptomatic group (0.34%) and the control group (0.22%) ($p=0.4844$). The MC rate of the runners who passed the “neck check” was 0.24% and the rate for the runners who failed the “neck check” was 0.26% ($p=0.9306$ vs. control group). The runners who experienced systemic symptoms during the 7 days prior to the race had a MC rate of 0.44% ($p=0.3782$ vs. control group).

Conclusion

The results of this study showed that most the common illnesses amongst runners are acute respiratory conditions (URT illness), followed by gastrointestinal disorders and then dermatological conditions. The period prevalence of runners with an acute illness one week prior to an endurance race was 19.2% and this is novel data, as no studies could be found in our review which indicated the period prevalence of runners with an acute illness 7 days

prior to an endurance race. The most common symptom of acute illness was a sore throat (34.5%).

A screening process and an educational intervention program resulted in a DNS rate that was significantly higher in the symptomatic group compared with the control groups, while the DNF and MC rates were similar between the two groups. This indicates that runners who reported symptoms of acute illness, and who were given educational information, had a significantly higher did-not-start (DNS) rate compared with control (no reported symptoms) runners. Runners who reported symptoms of acute illness, and who were given educational information but decided to start the race, had a similar did-not-finish (DNF) rate and medical complication (MC) rate compared to control runners. We suggest that the higher DNS rate in the symptomatic group was as a result of the educational information that was provided. We cautiously conclude that the educational information was effective in increasing the DNS rate in runners with more severe illness that could lead to a potential medical complication. It would also appear that those runners with pre-race symptoms who received the screening and educational information and then did start the race, despite a history of pre-race illness, did not have an increased risk.

We also noticed that 12.5% of runners reported symptoms that would result in a failed “neck check” and this may place these runners at a particular high risk of developing medical complications during a race. Current clinical guidelines indicate that an athlete who experiences systemic symptoms (i.e. failing the “neck check”), should not be allowed to exercise due to the possibility to develop a medical complication. In our study we showed that in sub-groups with a potential higher risk for medical complications, the DNS rate was higher: systemic symptom group (14.7%), failed “neck check” group (12.2%), and gastrointestinal symptom group (12.1%). These data indicate that a screening process can identify runners with acute illness symptoms, and that an educational intervention can be applied resulting in an increased rate of not

starting a race. We cautiously conclude that a screening and educational program may reduce the risk of developing medical complications during an endurance race.

Key words: neck check, exercise, illness, risk, prevention, complications, immune system

Chapter 1

Introduction and scope of the thesis

One of the most common clinical challenges a sport and exercise medicine physician encounters on a regular basis is whether an athlete is eligible to exercise or participate in a sports event while being acutely ill. This is a complex challenge, and a number of factors have to be considered:

- What puts the athlete at risk to develop an illness?
- How often does this occur in athletes?
- Does an acute illness negatively affect exercise performance?
- Are there any negative health consequences for the athlete if an incorrect decision is made?
- Is the clinical approach the same for all acute illnesses?
- Are there evidence-based guidelines to assist the clinician in making a correct clinical decision?
- Are there any preventative strategies to reduce the risk of acute illness in athletes?

This dissertation explores this area of sport and exercise medicine. In Chapter 2, a review of the existing literature that addresses these factors will be presented. The first section in this chapter will explore the epidemiology of acute pre-race illness, the relationship between exercise and pre-race illness, the risk factors for developing and acute upper respiratory tract (URT) illness in athletes, the relationship between exercise and the immune system, the common cause for acute illness in athletes and the effect of acute illness on the athlete's exercise performance. The second part of Chapter 2 will address the clinical aspects of acute URT illness, the return-to-play guidelines for acutely ill athletes, possible medical complications when exercising with an acute illness, and the possible preventative strategies that can be implemented in an attempt to prevent acute illness in athletes.

In Chapter 3 the results of an original research study are presented that was designed to address the following research question: “Does a screening and educational intervention program for acute illness before a distance race influence runner behaviour and result in a lower rate of inability to finish a race and medical complications during the race?” The aim of this prospective cohort study in 7035 runners was to determine 1) the period prevalence of runners with symptoms of an acute illness one week prior to an endurance race [the 2012 Two Oceans Race (21km and 56km)], 2) the period prevalence of runners who “fail” the “neck check” and would be advised not to participate in the race, 3) the incidence of runners with an acute illness, and who received educational information and guidelines, and who then not start the race, 4) the incidence of runners with an acute illness who chose to start the race, but do not finish the race, and 5) the incidence of runners with an acute illness who chose to start the race, but develop medical complications during the race. These data will provide some evidence if such a program makes racing with an acute illness safer for the athletes. To our knowledge, this is the first study where such an educational intervention program was utilized.

Finally, in Chapter 4, the results from this dissertation will be summarized and directions for future research will be explored.

Chapter 2

Acute pre-race illness in distance runners: A review of the epidemiology, risk factors, aetiology, clinical presentation and diagnosis, effects on performance, medical complications, return-to-play guidelines and prevention

2.1. Introduction

Acute illness, specifically infective illness, is a significant health concern for the elite athlete, the novice athlete, as well as the “weekend warrior” athlete who enjoys keeping fit and participating in sport. Apart from preventing an athlete from participating in important training sessions, an acute illness can also cause a decline in exercise performance or prevent the athlete from taking part in a competitive event, particularly when the athlete prepared for this event over months or even years. However, and most importantly, an acute infective illness can also increase the risk of medical complications and even sudden cardiac death during exercise ((1), (2), (3), (4)).

It has been documented that adults are affected, on average, by 1 to 6 episodes of an acute infection, mostly the “common cold”, per year. However, there is some evidence that elite athletes undergoing intense training may suffer from even more frequent episodes of acute infective illness (1). In recent years, it has also been documented in a number of epidemiological studies, that the most common system affected by acute illness in athletes is the respiratory tract, followed by the gastrointestinal system and then the dermatological system ((1), (5), (6), (7)). In this dissertation, the main focus will be on acute illness affecting the respiratory tract. The main reasons for choosing this focus are 1) this is the most common system that is affected by acute illness in athletes, and 2) this is also the system where most research data are available. Where appropriate,

specific reference will be made to acute illness affecting other systems such as the gastrointestinal, cardiovascular, and musculoskeletal systems.

When an athlete participates in a training session or competition while suffering from an acute illness, there are potential health consequences. These medical complications can include less serious and more serious life-threatening complications, or even sudden death (8). To date, sport and exercise medicine physicians and general practitioners have utilised a clinical guideline, known as the “neck check”, to determine if athletes with acute respiratory tract illness can participate safely in a training session or a competition (9). However, there is very little literature to support and validate this clinical guideline. The focus of this dissertation is on acute pre-race respiratory tract illness in distance runners. More specifically, the focus is on clinical guidelines to determine if runners can participate in an endurance event if they suffer from acute pre-race (7 days before the race) respiratory tract illness.

The aim of this chapter is to review the following aspects of acute illness in athletes with specific reference to acute pre-race illness in distance runners: 1) epidemiology, 2) risk factors, 3) aetiology, 4) clinical presentation and diagnosis, 4) effects on performance, 5) medical complications, 6) return-to-play guidelines, and 7) prevention.

2.2. Methodology of data acquisition

The principle method for data acquisition was in the form of a search of well-known databases for medical literature (including PubMed, EBSCO, and Medline) as well as Google Scholar. Potential publications were identified using the following keywords*: acute infections, running, distance running, marathon athletes, risk, neck check, exercise, and illness*. No specific date limitations were set. The primary aim was to identify publications with high-level evidence (level I and II), but lower level evidence (level III and IV), studies were also considered.

Study designs were determined and categorized according to the Oxford levels of evidence (Table 2.1.)

Table 2.1. Oxford levels of evidence (10)

Level of evidence	Study design
Level 1	• Systemic review of homogenous randomized control trial (RCT) • Individual RCT with narrow confidence level
Level 2	• Individual cohort study • Low quality RCT
Level 3	• Individual case-control studies • Non-consecutive cohort study
Level 4	• Case series
Level 5	• Expert opinions

2.3. Epidemiology of acute pre-race illness in distance runners

2.3.1. Introduction

In one of the earliest studies conducted to determine the risk of illness in distance runners, it was documented that 28% and 32% of runners entering the 1982 and 1983 Glasgow marathons respectively, did not start the race, and the main factor given for not starting the race was injury or illness (11). Since then, a number of epidemiological data suggested that endurance athletes are at increased risk for the development of URT illness during periods of intense training and in the 2 week period after marathon-type events ((2), (12), (13), (14), (15)). It has also been reported that there is a 100-500% increase in the risk of developing an URT illness in the weeks following an ultra-endurance running event (16), and 30-50% of athletes participating in endurance events such as marathon running will develop symptoms of an URT illness (8). However, the focus of this thesis is on pre-race illness; therefore, the remainder of this review will focus on pre-race illness affecting mainly the URT.

2.3.2. Period prevalence of acute pre-race URT illness in distance runners

To our knowledge, there are only a few studies that have been conducted to determine the relationship between upper respiratory tract (URT) illness prior to or after a distance running event. In one study the incidence of post-race URT illness was reported, and in two studies, the period prevalence of pre-and post-race illness was studied.

One of the first studies to report the relationship between a distance running event and the development of acute illness was a prospective cohort study conducted at the Two Oceans Ultra-marathon in Cape Town in 1982. In this prospective cohort study, the ***post-race*** period (14 days post-race) prevalence of symptoms of URT illness was reported in 150 randomly selected runners and compared to individually matched controls that did not run. Symptoms of URT illness occurred in 33.3% of runners in the 14-day post-race period, compared with 15.3% of controls that did not run. Furthermore, post-race symptoms were common in the athletes who achieved faster race times (17). However the epidemiology of pre-race illness was not investigated in this study.

To our knowledge, the first study to examine the relationship between distance running and pre- and post-race illness was conducted at the 1987 Los Angeles Marathon (14). In this epidemiological study, runners reported episodes of URT illness for the 8-week period before and the 1-week period after a marathon race. Notably, 40% of the runners reported at least one period of URT illness during the 8-week period before the marathon. Furthermore, distance trained per week was identified as a possible risk factor to develop an URT illness after a marathon.

In one other prospective cohort study the period prevalence of illness episodes were reported in the 3 weeks before and 3 weeks after the 2000 Stockholm Marathon (18). In this study of 1694 runners, 17% of runners reported an URT

illness in the 3-week period prior to the marathon. It should be noted that, although this was a random sample of all entrants, there was a significant dropout rate from the original cohort that was studied. Nevertheless, these data indicate that a significant percentage of runners experience pre-and post-race symptoms of acute URT illness.

It should be noted that in all these studies self-reported symptoms of illness were documented. It had always been assumed that these symptoms of URT illness were as a result of an infection, possibly resulting from a depressed immune system. However, this diagnosis is subjective and non-scientific, as there is evidence that these symptoms are not necessarily as a result of an infection. Further studies are needed to determine the cause of these symptoms that can include allergies ((8), (16), (19), (20)), pollution ((8), (16), (21)), airway hypersensitivity (19) and airway inflammation ((16), (20)).

2.3.3. Summary

In summary, there are few studies in which the period prevalence of pre-race acute illness has been studied in distance runners. However, data from two studies indicate that this is a significant medical problem with 40% of runners reporting acute URT illness in an 8-week pre-race period, and 17% reported pre-race URT illness in a 3-week pre-race period. It is also noted that in these studies, the acute pre-race illness was attributed to an infection, and this may not be valid. This will be explored in section 2.5 of this review.

2.4. Risk factors for acute URT illness in distance runners

Numerous risk factors for developing an acute URT illness have been identified. These can be broadly classified as either intrinsic (inherent to the athlete) or extrinsic (environmental and other factors). An in-depth review of these risk factors is beyond the scope of this dissertation, but the evidence that these

factors are associated with acute URT illness in athletes will now be briefly reviewed.

2.4.1. Intrinsic risk factors

2.4.1.1. Immune system depression

There is an extensive body of literature describing the relationship between exercise and the immune system – known as exercise immunology ((8),(12), (13), (16), (21)). A comprehensive review of this field is beyond the scope of this dissertation. However, there is strong evidence that changes in the immune system occur in response to acute bouts of exercise and prolonged training. Transient or more prolonged immune depression is also the basis of the pathophysiology and risk of acute illness in the exercising individual, including endurance athletes. Therefore, a brief overview and summary of the main changes in the immune system, as a result of participation in an acute exercise session or prolonged training, will now be presented. These changes in the immune system following exercise sessions or prolonged training are likely related to the other intrinsic and extrinsic risk factors, and these will also be reviewed briefly.

Immune system depression and a single exercise session

It has been well documented that there are changes in a variety of immune system component numbers and/ or functions following a single intensive exercise session. These changes include an increase in circulating neutrophils ((8), (16), (21)), a decrease in the lymphocytes ((8), (21)), a decrease in neutrophil function (oxidative activity and phagocytic capacity) for 1-3 days after the exercise session ((8), (13), (21)), a reduction in natural killer (NK) cell numbers and cytotoxic activity ((8), (16), (21)) and a decrease in the salivary IgA concentrations ((8), (12), (13), (21)).

There is an increase in the neutrophil: lymphocyte ratio (used as a predictor of stress to the immune system) for most of the following day after a heavy exercise session ((15), (21)). There is also an increase in pro- and anti-inflammatory cytokines (including interleukin-6 and interleukin-10) ((8), (13), (21)), an elevated concentration of T-helper 2 lymphocytes (8), and a shift towards type 2 T-cell dominance ((8), (16), (22), (23)).

A higher plasma concentration of several hormones (such as epinephrine, cortisol, growth hormone and prolactin) occurs after a heavy exercise session and acute phase proteins such as C-reactive protein (CRP) is induced ((16), (21)). A 20% reduction in plasma glutamine concentration may occur (21).

There is conflicting evidence regarding T-cell function. In some studies it has been documented that T-cell function declines after an intense exercise session ((13), (15), (21)), while other data indicate that the T-cell function does not change ((8), (12)).

A single bout of exercise thus results in changes in various immune parameters. These changes may last for 3-72 hours. This period is known as the “open window” period phenomenon during which time these changes in the immune system may predispose an athlete to viral and bacterial infections ((3), (8), (12), (13)).

Despite evidence that certain immunologic parameters change after an acute intense or prolonged exercise session, there is a lack of evidence to indicate that there is a direct link between the altered immune parameters and an increased incidence for URT illness symptoms post-exercise ((8), (9), (16), (21)).

Immune system depression and prolonged training

It has been documented that post-exercise immune dysfunction is most pronounced when the exercise session is more than 90 min long and the intensity is 55-75% of maximum oxygen uptake ($V0_2Max$) (16), while other data indicate that a session longer than 60 min at an intensity > 80% of maximum ability cause a depression in the immune system (8). It has also been shown that overtraining (daily training over a long period of time) leads to immune suppression which may render the athlete susceptible to an URT illness ((1), (24)).

Prolonged exercise (2.5 to 3 hours of intensive running) is associated with an increase in neutrophils (13), a decrease in lymphocytes ((13), (16)), an increase in neutrophil phagocytosis (13), and a decrease in natural killer cell activity (NKCA) ((13), (16)) that can last for 6 hours. The decrease in NKCA appears to be related to the decrease in the number of circulating NK-cells after prolonged training ((13), (16)). The neutrophil oxidative burst activity however show a small decrease ((12), (13)) and there are some evidence that plasma cortisol and epinephrine inhibit mitogen-induced lymphocyte proliferation (13).

T-cell function decrease for 3 hours after a 2.5 hour intensive running session (13) and salivary IgA decreases after 2 to 3 hours of intensive endurance exercise ((13), (21)). Following prolonged, strenuous exercise, the production of immunoglobulins by B lymphocytes is inhibited (16).

The mucosal immune system and the innate non-specific immune system together form the body's first line of defence against pathogenic organisms (8), as secretory IgA inhibits pathogens' attachment to the upper respiratory tract and thus prevent the entry of the pathogens into the body (12). It has been documented that salivary IgA is decreased after a prolonged or high intensity exercise session, increasing the athlete's risk to develop URT illness symptoms (23). A series of studies have also been conducted to document the immune responses of elite swimmers during training (20). These data show that

swimmers with a lower pre-season salivary IgA and/or lower pre-exercise salivary IgA concentrations had an increased risk to develop an URT illness during a 7-month training period, compared with controls.

Therefore, these data support the hypothesis that regular high-intensity or prolonged exercise bouts increase the risk of an URT illness, as prolonged training may result in chronically impaired immune function.

Summary: Immune system depression

It has been well documented that various components of the immune system are altered by acute bouts of prolonged, continuous exercise (Table 2.2.) There is however little evidence to link the specific exercise-induced changes to an increased incidence of URT illness in endurance athletes ((8), (13), (16).

Table 2.2. Changes in immune system components following acute bouts of prolonged continuous exercise

Component / component function	Perturbation
Lymphocyte count	Decrease
Neutrophil count	Increase
Neutrophil: lymphocyte ratio	Increase
Oxidative burst of neutrophils	Decrease
Neutrophil chemotaxis and phagocytosis	Decrease
NK cell count	Decrease
NKCA	Decrease
CRP	Induced
Salivary IgA	Decrease
Immune response	Shift towards T2 immune response
T-cell function	No consensus
B-cell function	Unchanged
Lymphocyte proliferation	Decrease
Monocyte count	Increase
Glutamine concentration	Decreased

NK (Natural killer)
NKCA (Natural killer cell activity)
CRP (C-reactive protein)

2.4.1.2. A history of a recent URT illness

There is some evidence that a history of a recent acute illness may predispose an athlete to an increased risk of illness. In one prospective cohort study conducted during the Stockholm Marathon, 33% of athletes who experienced an URT illness in the 3-week period prior to the race developed an URT illness in the 3-week period after the race (18). This was significantly greater than the 16% of athletes who did not have an URT illness prior to the marathon. These data suggest that strenuous exercise too soon after an acute illness may be a risk factor to develop a subsequent illness. However, these data have not been linked to specific changes in the immune function (section 2.4.1.1.) in athletes who return to exercise training following acute illness. As this is also the only study

relating previous acute illness to increased risk of illness, this area requires further study.

2.4.1.3. Female gender

There is some evidence to suggest that female athletes are at higher risk of an acute illness. In one prospective cohort study, 210 endurance athletes (63 females and 147 males) completed a self-report health questionnaire on a daily basis for 16 weeks (25). It was documented that the proportion of participants who experienced one or more periods of URT illness symptoms, was 40% in males and 52% in females. The mean duration of URT illness symptoms was also longer in female athletes (15.5 days) compared to the males (11.6 days) ($p=0.024$), and the number of URT illness symptoms days were higher in females (6.8 days) than in males (4.7 days) ($p=0.016$).

In the International Olympic Committee's injury and illness surveillance study conducted at the 2012 Winter Youth Olympic Games held in Innsbruck (N=1021), it was reported that the incidence of acute illness was 84.2 illnesses per 1000 athletes (6). With regard to gender, 6% of male athletes and 11% of female athletes suffered from an illness ($p=0.003$). A similar finding was documented during the 2012 Summer Olympic Games held in London, where a daily injury and illness occurrence was recorded (5). The illness incidence was 71.7 illnesses per 1000 athletes and females had a higher incidence if illness compared with male athletes (8.6% vs. 5.3%). Therefore, a number of studies indicate that female gender is a risk factor for acute illness in athletes, but this requires further investigation.

2.4.1.4. Increased body mass index (BMI)

There is some evidence that an increased BMI is associated with increased risk of acute illness in athletes. In one prospective cohort study, illness patterns were

studied in 530 male and female runners who completed a monthly log for 12 months. The results of this study show that a BMI > than the 75th percentile was associated with an increased risk to develop an URT illness (26). Therefore, there are data to suggest that an increased BMI increases a runner's risk to develop an URT illness, but this needs to be verified by more studies.

2.4.2. Extrinsic risk factors

2.4.2.1. Increased training load

It has been documented that sedentary individuals have a higher incidence of symptoms of URT illness compared with individuals who engage in regular moderate exercise (50-70% of maximum ability, 30-60 minutes per session, 3-5 sessions per week) (8). It has also been documented that regular intense and prolonged exercise bouts may increase an individual's risk to develop and URT illness, as such training may result in a chronic depression of the immune system (section 2.4.1.1.).

The relationship between the training load ("dose") of exercise and the risk of URT illness symptoms is commonly reported as a "J-shaped" curve ((2), (3), (8), (12), (15), (16), (21), (23)) (Figure 2.1.)

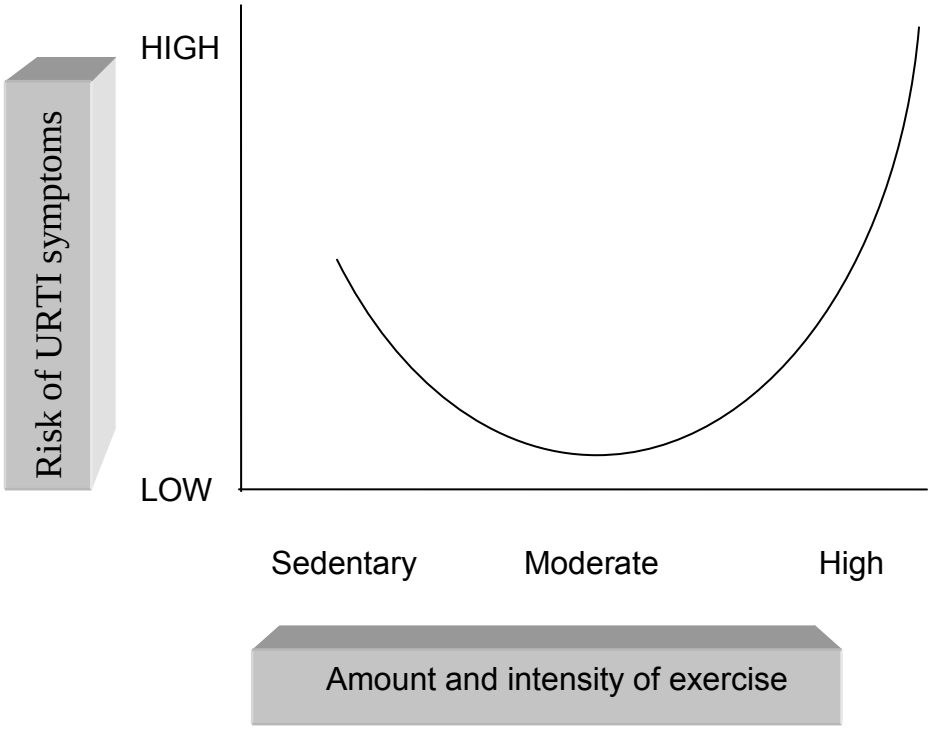

Figure 2.1. The "J-shaped" model depicting the relationship between varying amounts of exercise and the risk of developing URT symptoms

Data from a number of well-conducted studies support this "J-shaped" model for the relationship between exercise and the susceptibility to acute URT illness. It has been documented that in one randomized control trial, 36 woman walked briskly for 45 min, 5 days per week for a 15-week period (15). The results of the study showed that active woman experienced symptoms of URT illness on 5.1 days during this 15-week period, compared to the sedentary control group who experienced symptoms of URT illness on 10.8 days ($p<0.05$). It has also been documented that in another randomized trial, elderly woman were monitored over a 12-week period (15). Women who walked 40 min, five times per week, had a 12-week incidence of URT illness of 21% compared with 50% for a sedentary control group (15).

In an observational study of 547 healthy adults (49% women) aged 20-70 years, URT illness events were reported at 90-day intervals over a 12-month period (5

evaluations) (23). Three 24-hour physical activity recalls per evaluation were obtained and averaged to quantify total moderate-vigorous activity (> or =3.0 metabolic equivalents [MET]). Associations between URT illness and physical activity levels were estimated using incidence rate ratios (IRR). The results indicated a 29% reduction in the incidence rate of URT illness symptoms in adult men and women who engaged in moderate physical activity of at least 6-7 metabolic equivalents (METS) per hour per day, when compared to individuals who were less active.

In summary, data from well-conducted studies (level 1 and 2) support the hypothesis that sedentary individuals have a higher incidence of URT illness symptoms compared to people who exercise at a moderate intensity or duration.

However, in runners training more than 97 kilometres (km) per week, there was a two-fold increased risk for developing an URT illness compared to runners who trained less than 32 km/week (14). These data suggest that strenuous training increases the risk for developing an URT illness. In one prospective cohort study, illness patterns were studied in a cohort of 530 male and female runners who completed a monthly log for 12 months (26). It was shown that runners who exceeded 777-1385 km (486-866 miles) during the 12-month period had a significantly higher risk of developing URT illness symptoms. Epidemiological data from studies on South African ultra-marathon runners also indicate that “heavy” acute or chronic exercise is associated with an increased risk of URT illnesses (15).

However, it is very important to note that the “J-shaped model” is mostly based on studies that only examined self-reported symptoms that are associated with URT illness and not clinically diagnosed infections with a specific pathogen. This has led to some researches questioning the validity of this model (23).

In only one prospective cohort study there are data to support the “J”-shape hypothesis for documented URT infection (19). In this study, 32 elite athletes, 31 recreational athletes and 20 sedentary individuals were followed over a 5-month period. Individuals who reported symptoms of URT illness were tested with throat and nasopharyngeal swabs for the presence of viral and bacterial pathogens. Nine sedentary, 7 recreational and 21 elite athletes developed an URT infection (37 URT infections in 28 subjects). Although actual pathogens were only found in less than 30% of all the cases, these data support the J-shaped hypothesis. However, these data also indicate that both infectious and non-infectious (allergic reactions, airway hypersensitivity and other causes) causes for URT illness should be considered when an athlete presents with symptoms of URT illness.

In the studies mentioned above, there was no clear distinction between the different components that define an “increased” or “heavy” training load. The main components determining training load are duration of exercise, frequency of training, and intensity of exercise. In a number of studies, duration and frequency are frequently combined as training volume (daily, weekly, or annual). The specific relationship between these components and risk of URT illness in runners will now be briefly explored. It should be noted however that there are very few studies where the relationship between URT illness and these components of training load have been reported.

Training volume and risk of URT illness

In one epidemiological study, it was documented that athletes who trained more than 96km/week for the Los Angeles Marathon, had a > 2 fold increased risk of developing an URT illness when compared to athletes who trained less than 32km/week (14). In a prospective cohort study, it was shown that an annual training distance > 777km (486 miles) was a risk factor for developing an URT illness (26). It has also been documented that training volume > 65km/week was a risk factor for developing an URT illness (8). The mechanism of this appears

may be related to a reduction in immune system function as a result of prolonged training.

Intensity of exercise and risk of URT illness

To our knowledge, there are no epidemiological data relating training at increased intensity to an increased risk of acute illness – including URT illness. However, there are data indicating that immune dysfunction is most pronounced in athletes who train at a higher exercise intensity (50-75% of maximal oxygen uptake) (16). Other data indicate that an exercise intensity level greater than 80% of maximum ability is associated with a depressed immune system (8). In summary, there is some evidence that increased training intensity is associated with a reduction in immune function that may increase the risk of developing URT illness in distance runners.

2.4.2.2. Nutritional factors

The relationship between nutritional factors and increased risk of URT illness in endurance athletes has also been explored. In general, immune cells require an adequate amount of glucose, protein, water and electrolytes to maintain normal function (21). Therefore, a well-balanced diet is important for immune function. A detailed exploration of the relationship between multiple nutritional factors and the immune system is beyond the scope of this dissertation. However, in a review of 66 placebo-controlled and/or crossover trials, it was concluded that a poor nutrition state affects almost all aspects of the immune system (21). More specifically, an unbalanced diet (a high carbohydrate (CHO) intake at the expense of protein), training in a dehydrated state, and the excessive use of nutritional supplements may lead to negative effects on the immune function in athletes (21).

In addition, glucose is considered to be an important fuel substrate for various immune cells, including macrophages, lymphocytes and neutrophils. There is some evidence that frequent ingestion of a ≥ 6% CHO solution (1 litre per/hour) during prolonged or high intensity exercise maintains blood glucose levels, which lead to an attenuated post-exercise cortisol level, resulting in a less suppressed immune function. The ingestion of the CHO may also attenuate exercise-induced increases in the total leucocyte count and/or leucocyte subsets such as monocytes and neutrophils, and cytokine changes, which usually leads to a decreased immune function (21).

Finally, it has been documented that the immune function is suppressed during periods of low calorie intake and weight loss (15), and data show that inadequate nutrition and exercising without food intake may contribute to an impaired immunity, which makes the individual more susceptible to infection (21).

2.4.2.3. Other extrinsic risk factors

Inadequate recovery from training

It has been documented that a single bout of strenuous exercise (a prolonged session at high intensity) is followed by a period of temporary immune suppression ((2), (8), (12), (16), (21)). As mentioned already, this has been termed the “open window” period ((2), (8), (12), (21)), and during this post-exercise period, a runner may be more susceptible to infections. If sufficient resting periods between strenuous exercise sessions are not allowed, the athlete is at an increased risk to develop an URT illness, as the immune function has insufficient time to recover from the perturbations caused by the strenuous exercise session ((2), (3), (8)). Therefore, inadequate recovery after strenuous exercise session may be an important risk factor for acute illness. Increased risk of illness has also been related to fatigue (2), and overtraining ((1), (2), (8)).

Poor sleep and increased psychological stress

There is evidence that other extrinsic factors such as alterations in normal sleep patterns and psychological stress can increase the risk of acute illness ((15), (21)). A summary of risk factors for developing an URT illness is depicted in Table 2.3.

Table 2.3. Risk factors for developing an URT illness

	Risk factor	Variable
Intrinsic	Immune system	Depression of a number of immune system components
	Medical history	History of recent URT illness
	Gender	Female
	BMI	BMI > 75th percentile
Extrinsic	Training volume	>97km / week >65km / week
	Training intensity	>80% of maximum ability
	Nutrition	Inadequate CHO intake Inadequate calorie intake Exercise in dehydrated state Exercise without food intake
	Other extrinsic factors	Inadequate recovery time between heavy exercise bouts Poor sleep Psychological stress Overtraining

2.5 Aetiology of acute URT illness in athletes

An URT illness can be defined as clinical symptoms and signs affecting the upper respiratory tract as a result of a either infective or non-infective cause. An URT infection can be defined as an acute illness affecting the nasopharynx, caused by microbial agents, and resulting in local and sometimes systemic symptoms. A detailed review of the aetiology, microbiology and pathophysiology

of acute URT illness is beyond the scope of this dissertation. However, it is well documented that infective URT illness is most commonly caused by viruses (8), but can also be caused by bacteria and fungi. There are more than 200 different viruses causing colds, and the rhinoviruses and coronaviruses are the pathogens in 25-60% of the time (12). The most common viruses causing various URT and related infections are depicted in Table 2.4.

Table 2.4. Most common viral causes for URT and related infections

Disease	Organism
Common cold	Rhinovirus Coronavirus Echovirus Coxsackie B
Influenza	Influenza (ABC)
URT infection	Adenovirus Parainfluenza Coxsackie A Respiratory syncytial virus
Lower respiratory tract infection	Adenovirus Respiratory syncytial virus
Infectious mononucleosis	Ebstein-Barr virus

Rhinovirus infections usually occur during spring and autumn, while infections are commonly caused by the coronavirus during winter time (12). The most common virus involved in URT infection is the rhinovirus (19). A viral infection usually lasts for 3 to 14 days.

As mentioned, URT illness symptoms are not always due to an URT infection caused by the common viruses or bacteria. In one prospective study performed on elite athletes, it was shown that pathogens were identified in less than 30% of athletes who reported symptoms of an URT illness (19). In 2 other studies, cultures were taken from athletes who complained about URT illness symptoms after an ultra-marathon race. The cultures showed no growth (8). Therefore, other systemic infectious and non-infectious conditions should be considered

when an athlete presents with symptoms of an “URT infection” ((27), (28)). These causes are summarised in Table 2.5.

Table 2.5. Infectious and non-infectious causes of URT illness symptoms

Sub-group	Condition
Systemic infectious conditions	• Infectious mononucleosis • Tuberculosis • Systemic infections (rubella, chickenpox etc.) • Ludwig’s angina
Non-infectious conditions	• Allergic rhinitis • Asthma • Wegener’s granulomatosis (type of vasculitis) • • Gastro-oesophageal reflux disease • Obstructive sleep apnoea • Acute thyroiditis

Of these conditions, allergic rhinitis is one of the most common conditions that can mimic an URT infection. It is important to note that by taking a thorough history, and conducting a clinical examination, allergic rhinitis can be differentiated from an URT infection.

In summary, URT illness symptoms can be due to infectious and non-infectious causes. Viruses most commonly cause infectious URT illnesses and the most commonly implicated virus is the rhinovirus, followed by the coronavirus. Non-infectious URT illness symptoms are most commonly caused by an allergic rhinitis, and taking a thorough history and performing a good physical examination can usually distinguish between an URT infection and allergic rhinitis. The clinical presentation and diagnosis of acute URT illness will now be briefly reviewed.

2.6. Clinical presentation and diagnosis of acute URT illness in athletes

2.6.1. Symptoms and signs of an URT illness

Symptoms of an URT infection can be divided into localised and systemic symptoms. Localised symptoms will include a blocked or runny nose, sore or scratchy throat, sinus congestion and sneezing. Systemic symptoms include fever, malaise, myalgia (muscle pain), arthralgia (joint pain), lymphadenopathy, coughing and an increased resting heart rate. It is important to differentiate between localised and systemic symptoms, as these symptoms form the basis of the “neck check” guideline that has been proposed and is utilised by physicians to advise athletes with symptoms of an acute URT illness on participation in sport ((1), (2), (9)). Specifically, these clinical guidelines suggest that athletes who have systemic symptoms are not eligible to exercise.

A thorough clinical examination is important as more serious conditions can mimic an URT illness. Signs on clinical examination can also be divided into localised and systemic physical signs. Local signs include tenderness over the sinuses, throat erythema and nasal mucosa engorgement while systemic signs include lymphadenopathy, tachycardia, fever, and rhonchi or crepitations in the lungs.

It is important to note that there are other infective conditions that can mimic a localized viral URT infection. Infectious mononucleosis (IM) is one of these conditions and can present in the same manner as pharyngitis (sore throat, lymphadenopathy and fever). An enlarged spleen (which can be difficult to palpate) might be the only clinical indication that the athlete has IM. This has consequences for the return to play guidelines (as discussed in Section 2.9).

Myocarditis is another condition that can initially present with similar clinical characteristics to an URT illness (fatigue, malaise, fever, myalgia and palpitations). A tachycardia out of proportion to the degree of pyrexia, a muffled 1st heart sound and apical systolic murmur are clinical signs that may direct the clinician towards a clinical suspicion of myocarditis (8).

2.6.2. Special investigations

Special investigations are very seldom performed in an uncomplicated URT illness, as the cause is usually a virus. Viral cultures and polymerase chain reaction (PCR) tests are only indicated in patients for whom specific anti-viral therapy is recommended. A pharyngeal swab for rapid antigen detection of group A beta-haemolytic streptococci can be performed, and this test is 90% sensitive and 95% specific in adults. However, an antistreptolysin O test is generally not helpful in the acute illness and is usually only detected several days after an infection began (27).

Special investigations are also indicated when other viral conditions mimicking an uncomplicated URT illness are suspected. One such condition is infectious mononucleosis (IM). When IM is suspected, a full blood count (FBC) can be performed that may show an elevated white cell count (WCC) with atypical lymphocytes accounting for up to 30% of the differential WCC. The presence of heterophile antibodies (Monospot test) may confirm the diagnosis in 85-90% of cases. The Epstein-Barr virus antibodies are both specific and sensitive for Epstein-Barr infection and the capsid antigen IgM is usually positive. An ultrasound of the abdomen may show splenomegaly (8). Allergic rhinitis is another condition that may cause symptoms of URT illness, and an elevated IgE will direct the clinician towards an allergy related URT illness.

Myocarditis is an important complication that may be associated with acute URT illness. If myocarditis is suspected, a Troponin T and Troponin I blood test should

be performed, as well as an ECG and echocardiogram (8). Viral myocarditis and myopericarditis are discussed in section 2.8.1 and section 2.8.2.

When a Coxsackie virus is suspected, Coxsackie antibodies can be tested. The results will be given as titres for several of the Coxsackie viruses and, if indicated, the IgM for a specific Coxsackie virus can then be requested.

In summary, a number of special investigations can be requested to confirm the diagnosis of specific conditions that can cause URT illness (Table 2.6.)

Table 2.6. Indications for special investigations in URT illnesses

Special investigation	Indication
Viral cultures and PCR	Specific anti-viral therapy is recommended
Pharyngeal swab – rapid antigen detection	Group A β-haemolytic streptococci suspected
FBC Monospot test Ultrasound of abdomen	Infectious mononucleosis suspected
Troponin T Troponin I ECG Echocardiography	Viral myocarditis suspected
Coxsackie anti-bodies	Coxsackie virus suspected
Serum IgE	Allergic rhinitis suspected

2.7. Effects of acute URT illness on exercise performance

2.7.1. Introduction

Infections, including URT infections, and / or bed rest (which is part of the treatment of most infections), can influence several organ systems and physiological parameters in the body. Acute febrile infections are associated with circulatory deregulation, muscle wasting, impaired motor coordination (3), a

decrease in muscle strength and endurance, an inability for the body to regulate body temperature, a reduction in exercise tolerance, and an increase fatigability (2). This can have consequences for the athlete's exercise performance. It has been documented that even a minor infections can cause a decrease in exercise performance and reduce the ability to sustain high intensity or prolonged training (16).

Many athletes regularly experience a sudden and unexplained decrease in exercise performance. Physiological fatigue should be excluded first and this includes overreaching, inadequate sleep, dietary causes, jet lag, pregnancy, and depleted iron stores. However, once it has been established that the athlete may suffer from a pathological fatigue and no obvious pathology can be found in any of the systems, a recent viral infection should be suspected (15). Infections that are subclinical in the non-athletic population may affect maximum exercise performance in athletes (29). Furthermore, athletes often complain about a decrease in exercise performance once in the recovery period following an URT infection. It has been documented that this decrease in exercise performance after full clinical recovery from an URT illness can last for 2 to 4 days (8).

In four different case reports, athletes complained of loss of stamina, inability to maintain their normal training load, tiredness and a decrease in exercise performance (29). Laboratory results indicated that 2 of the athletes had recent Coxsackie infections, one had infectious mononucleosis and the 4th athlete had recent infectious mononucleosis. It is worth taking note that 2 of these athletes had only minor symptoms of URT infections, and the other 2 athletes had no prodromal symptoms.

Apart from the general effects of a febrile illness on exercise performance, a number of specific organ systems can be affected by an acute illness. The effect of acute illness on these systems, and the relationship to reduced exercise performance will now be briefly reviewed.

2.7.2. Neurological system

A febrile infective illness can affect the nervous system and this can lead to an impairment of coordination. In one study, 14 participants with influenza or echovirus infection, all suffering from myalgia, and 9 participants with mumps, in whom this symptom was lacking, were investigated with single-fibre electromyography (EMG) in the acute phase and during convalescence to reveal a possible disturbance in neuromuscular transmission (3). The results showed that both groups had abnormal neuromuscular transmission characteristics in the acute phase. This study demonstrates that acute febrile infections may lead to reduced neuromuscular transmission in the motor-endplate during the early phase.

In another prototype experimental viral infection, isometric muscular strength and endurance of 10 male participants was measured four times per day for 15 consecutive days (3). Eight experimental participants were inoculated with the sandfly fever virus and two double-blind controls were given sterile saline on the seventh day. The muscular performances of the control participants remained constant throughout, whilst a decrease in muscular strength and endurance speed, and a decrease in coordination in the performance of motor skills at submaximal force was observed in the inoculated group (3). Although no data are available to link these changes causally to exercise performance, altered neuromuscular control may increase the risk of ankle injuries in certain sports (3).

2.7.3. Musculoskeletal system

There is evidence that abnormalities of skeletal muscles occur in patients with viral infections (30). Mitochondrial abnormalities have been reported during an infectious episode (12), a reduction in muscle enzyme activity (glyceraldehyde

phosphate, lactate dehydrogenase, cytochrome oxidase and citrate synthetase) has been documented (1), and it has been shown that infections cause a decrease in the protein content of the skeletal muscle, leading to muscle wasting (3). The decline in muscle strength and endurance from the athlete's baseline is correlated to the muscle protein loss caused by the infection (3), but it should also be noted that fever *per se* cause a decrease in muscle strength (1). It has been documented that both isometric and isotonic muscle strength decreased by 30% on the first day of fever in an experimental sandfly fever (3). Although muscle biopsies showed no significant muscle protein degradation at that stage, the magnitude of the impairment significantly correlated with the participant's ratings of subjective symptoms, including myalgia.

Following a flu-like illness with fever that lasted about 36 hours, it may take as long as 2 weeks to replenish the accumulated muscle protein losses. This period is much longer in more severe infections, such as malaria (3).

In summary, there is evidence that infection leads to a decrease in muscle protein content (which correlates to a decline in muscle strength and endurance), a reduction in muscle enzyme activity and mitochondrial abnormalities. It might take up to 2 weeks for the muscle protein to be replenished. Fever also causes a decrease in muscle strength. Therefore, it appears that a febrile illness negatively influences the ability to perform muscle work (3), and this may explain the decrease in exercise performance experienced by athletes after an URT infection (30).

2.7.4. Cardiovascular system

The normal physiology of the cardiovascular system, in response to an acute exercise bout, can be affected during acute febrile illness. It has been documented that fever reduces stroke volume and hence cardiac output, which correlates significantly with the severity of the fever (1). At the same time, fever

increase oxygen consumption and heart rate: for every 1°C the body temperature rise above 37°C, there is a 13% increase in oxygen consumption, and for every 1.5°C increase in body temperature, the heart rate increase by 2.44 beats per minute (1).

It has been documented that during an infection, which requires bed rest, the aerobic exercise capacity (as determined from the heart rate response during submaximal exercise) can decrease by as much as 25% (3). This response has been attributed to the negative influence that an infection can have on the blood volume, total haemoglobin, myocardial function and peripheral factors i.e. the changes in the skeletal muscles caused by the infection (see section 2.7.3) (3). Of note, there are data indicating that low intensity physical activity during an infection, such as getting out of the bed every half-hour during waking hours, resulted in a smaller blood volume reduction and a smaller decrease in aerobic capacity compared to conventional bed rest (3).

In one case study, data in an elite athlete engaged in a longitudinal program of physiological assessment, was reported (31). In this study, the athlete suffered a loss of performance as a result of a viral infection. During a prolonged submaximal exercise test in the post-viral period, there was a pronounced increased in the heart rate and perceived exertion ratings that led to the earlier termination of the test. The increased heart rate also influenced the graded exercise test and the cyclist could only complete 4 of the 6 stages. This is anecdotal evidence and further studies are required in this field.

In summary, there is some evidence to indicate that a febrile illness decreases the blood volume, total haemoglobin, stroke volume and cardiac output, and increases the oxygen consumption. These changes can lead to as much as a 25% reduction in endurance capacity. Some evidence exists to indicate that an infection also leads to an increased heart rate during submaximal exercise testing.

2.7.5. Thermoregulation

It is well established that a febrile illness affects the body's ability to regulate body temperature (2). As a result, this can increase fluid losses, which may put the athlete at a greater risk for dehydration and heat stroke (2).

2.7.6. Respiratory system

There is some conflicting evidence on the effect that an URT illness might have on the pulmonary system during periods of exertion. In one study the impact of a rhinovirus-caused URT infection on resting pulmonary function, submaximal exercise response, and maximal exercise functional capacity, was determined (32). The study consisted of 55 participants who were divided into a control group (N=10) and experimental group (N=45). All participants completed a baseline pulmonary function test and a graded exercise test to volitional fatigue after which the experimental group's participants were inoculated with rhinovirus-16 on 2 consecutive days. The day following the second inoculation, post-inoculation pulmonary function and graded exercise tests were performed on both groups. It was shown that, during the graded exercise test, there was no significant differences ($p<0.05$) in the physiological response measured at the 2, 5, and 8 minute periods between the running trials for both the experimental group and control group. There was also no significant difference in the maximal exercise performance between the two groups. It thus appears that the physiological responses to pulmonary function testing at submaximal and maximal exercise are not altered by an URT infection.

It has been documented that 3 studies were conducted on the effect of an URT illness on the pulmonary function of participants at *rest* (1). An impairment of peak expiratory flow rate, forced vital capacity, forced expiratory volume in 1 second, and maximal mid-expiratory flow rate, measured at 50% of vital capacity,

was documented, but changes in the maximal expiratory flow rate measured at 75% of vital capacity were not significant.

It has also been documented that a study on respiratory muscle strength in 12 participants who developed an URT illness showed that maximum static respiratory mouth pressures was significantly reduced during the infection (1). The greatest reduction was documented between the 3rd and 7th day of illness and returned to normal by day 14. The authors concluded that weakness of the inspiratory muscles might contribute to breathlessness of athletes during exertion whilst having an URT illness. Exercising during an on-going URT infection may cause bronchial hyperactivity (3).

In conclusion, there are some evidence that an URT illness has a negative effect on the peak expiratory flow rate, forced vital capacity, forced expiratory volume in 1 second, and maximal mid-expiratory flow rate, measured at 50% of vital capacity. These studies were however performed on participants at rest and studies performed on exercising participants showed that the pulmonary system is not affected by an URT illness during exertion, except that athletes might develop bronchial hyperactivity. More studies on exercising individuals with an URT illness are required in this field.

2.7.7. Immune and metabolic responses

Acute infections can also influence the normal physiological metabolic response to exercise. An acute infection activates macrophages and monocytes of the immune system. These cells release cytokines, which trigger an acute phase response (3). This non-specific cytokine-mediated response causes a shift in the metabolism in order to mobilise nutrients from the body tissues, predominantly amino acids from muscle tissues, to satisfy the increased nutritional needs of the activated immune system and to provide substrates for the accelerated energy production during fever (3). A feature of the acute phase reaction is thus the

induction of a generalized catabolism of muscle protein, as cytokines mediate the release of amino acids from the muscles and increased uptake of amino acids in the liver and other organs. As long as 2 weeks is required for the accumulated muscle protein losses to be replenished (3).

Hormones that regulate carbohydrate (CHO) metabolism are intimately involved in the host defence response to infectious illnesses. A viral illness results in hyper-insulinaemia and a decrease in carbohydrate tolerance. This is possibly due to elevated levels of hormones antagonistic to insulin. These include glucagon, cortisol and growth hormone. The combined effects of the hormones cause a decrease in glucose storage, which can result in a depletion of tissue CHO during an illness. When an individual then exercise whilst being ill, hypoglycaemia can develop, as glucose in the blood will be oxidised at an accelerated level and less liver glycogen will be available to mobilise (31). The elevated insulin levels during an infection and fever also generally reduce the mobilisation of fatty acids from the fat stores (3), and the resting levels of serum fatty acids are known to be lowered in severe acute viral infections (31).

In a case study on a 24 year old male elite cyclist who suffered a decrease in exercise performance after a viral illness, repeated measures indicated that the oxygen uptake equivalent to the onset of blood lactate accumulation of 4mmol per litre decreased by 17% following the viral illness, then slowly recovered (31). It was also indicated that, during prolonged exercise at 70% of VO_2max, the proportion of energy derived from CHO metabolism increased, and an inability to maintain euglycaemia was observed (blood glucose decreased after 60 min of exercise). The blood lactate values were also significantly higher at all stages during a graded exercise test after the infection compared to tests before the infection. The authors was of the opinion that this could be either due to an accelerated flux through glycolysis, or a decrease in the rate of entry of pyruvate for mitochondrial oxidation. Although there is insufficient evidence in this case study, the increased blood lactate levels could have resulted from an abnormal

oxidative capacity of the muscles due to the viral infection, thereby requiring a greater contribution from anaerobic glycolysis to maintain the rate of adenosine triphosphate (ATP) production (31).

It has been documented that a study was performed to determine the effect of viral and mycoplasma infections on the ultrastructure and enzyme activities in human skeletal muscle (1). For this, muscle biopsies were obtained from patients recovering from recent viral illnesses. The results of this study show that there was a significant reduction in muscle enzyme activity (glyceraldehyde phosphate, lactate dehydrogenase, cytochrome oxidase, and citrate synthetase). The muscle biopsies were repeated 3 months later, at which time these changes had almost completely resolved.

In summary, acute infection mobilise nutrients, pronominally amino acids from skeletal muscle, to satisfy the nutritional requirements of the activated immune system. A viral infection also causes an increase in glucagon, cortisol and growth hormone, which results in a decreased CHO tolerance and hyper-insulineamia. The increased insulin levels reduce the metabolism of fatty acids from the fat stores. There is also evidence to indicate that a viral infection causes a significant reduction in muscle enzyme activity.

There is some evidence that the oxygen uptake equivalent to the onset of blood lactate accumulation of 4mmol per litre decreased by 17% following the viral illness. During prolonged exercise at 70% of VO_2max, the proportion of energy derived from CHO metabolism increased and an inability to maintain euglycaemia was observed. The blood lactate values were also significantly higher at all stages during a graded exercise test.

2.7.8. Summary: Effects of acute URT illness on exercise performance

The effects of an acute URT illness on exercise performance in different organ systems are summarized in Table 2.7.

Table 2.7. Influence of acute illness on systems of the body, which lead to a decrease in exercise performance

System	Influence
Musculoskeletal	Muscle wasting (decrease in protein content) Decrease in muscle strength (isometric and isotonic) Decrease in muscle endurance Mitochondrial abnormalities
Cardiovascular	Decrease in aerobic exercise capacity Increase in heart rate at submaximal exercise intensity Decrease in stroke volume → Decrease in cardiac output
Neurological	Impairs motor coordination Decreased neuromuscular transmission
Metabolism	Catabolism of muscle protein Increased uptake of amino acids in the liver and other organs Decrease in muscle enzyme activity Decreased levels of serum fatty acids Decreased mobilisation of fatty acids from the fat deports Increase in the proportion of energy arriving from CHO metabolism Higher lactate levels at all stages during a graded exercise test Increase in glucagon, growth hormone and cortisol Hyper-insulinemia Decrease in oxygen uptake Inability to maintain euglycemia

In summary, an acute URT illness can affect a number of organ systems and result in a reduction in exercise performance. Specific detrimental effects on tissue structure and function include muscle wasting, impaired motor coordination, a decrease in muscle strength (isotonic and isometric) and endurance, a decrease in oxygen uptake equivalent to the onset of blood lactate accumulation of 4mmol per litre, an inability to maintain euglycemia, increase in blood lactate levels, a decrease in aerobic exercise capacity and an increase in fatigability. Furthermore, the presence of fever cause a decrease in the body's

ability to regulate temperature, increase fluid losses, decrease stroke volume and cardiac output and increase oxygen consumption.

In addition, there is temporary impairment in muscular and cardiovascular capacity during exercise (3). It is important for the treating physician and the athlete to understand that these and other changes may increase the risk of a medical complication if physical exercise is undertaken whilst suffering from an acute illness. The medical complications associated with exercise whilst suffering from an acute URT illness will now be reviewed.

2.8. Medical complications and risks associated with exercise training or competition in athletes with acute URT illness

A number of medical complications can occur in an athlete who performs physical exercise (training or competition) whilst suffering from an acute URT illness. These complications can vary from a reduction in exercise performance (reviewed in section 2.7.), or an increased risk of serious complications, including sudden death. It is well documented that sudden death can occur in young healthy people who exercised during acute viral illnesses (1). These medical complications, which are very important to consider when a treating physician advises an athlete whether to continue to exercise with an acute infection, will now be briefly reviewed.

2.8.1. Viral myocarditis

Myocarditis is defined as inflammation of the myocardium. Although the Coxsackie virus is the most common aetiological factor, and is responsible for approximately 50% of cases of viral myocarditis, other viruses including the rhinovirus, coronavirus, influenza and cytomegalovirus can also cause myocarditis. Bacteria, including the β-haemolytic streptococci, *Mycoplasma pneumonia* and *Chlamydia pneumonia* can also cause myocarditis. Myocarditis

can also be associated with infectious mononucleosis and can also occur as a complication after gastroenteritis (3).

The infection may solely affect the heart muscle, or the myocarditis may be part of an infection elsewhere in the body, or the myocarditis can be a complication of an infection elsewhere in the body. Most commonly, these infections are in the upper respiratory tract or digestive system (3). In experimental studies using Coxsackie virus mice models, it was found that the myocardial tissue was partly affected by the replicating virus, which cause cytolysis and subsequent scavenging of infected cells by virus-specific cytotoxic T-cells, and partly affected by the action of cross-reactive (autoimmune) cytotoxic T-cells. The infected myocardial cells may also cause a shutdown of the metabolism in adjacent non-infected cells by means of a toxic metabolite (3).

It has been documented that in mice, exercise stress during the early phase of Coxsackie myocarditis was associated with an increase in the replication rate of the virus within the myocardial cells ((3), (15)). This resulted in an increase in tissue damage due to cytolysis, and an enhancement in the immune mechanisms, resulting in an increased inflammatory lesion and necrosis (3).

In the majority of cases, myocarditis appears to be subclinical (the patient experiences no cardiac symptoms) and a reduction in exercise performance might be the only presenting symptom. This subclinical complication of infections can be aggravated by physical exertion (3).

Often symptoms of viral myocarditis are vague and non-specific, and can include fatigue, fever, myalgia, dyspnoea, chest discomfort (8), a sharp chest pain which becomes worse on deep inspiration, chest pain which radiates to the jaw, left shoulder and arm and palpitations (most commonly due to ventricular extra-systoles). An uncommon presentation includes acute congestive heart failure and sudden death (3).

The findings on physical examination are usually also very non-specific. General signs of a viral infection might be present. A tachycardia that is out of proportion to the degree of pyrexia is a useful indicator of possible myocardial involvement. On cardiac auscultation, the first heart sound may be muffled and an apical systolic murmur may be present (8).

There are a number of special investigations that might help with the diagnosis. The electrocardiogram (ECG) may show evolving ST-T changes on serial recordings (3) a heart block, ventricular arrhythmias, or findings mimicking a myocardial infarction (33). Serum concentrations of Troponin T and Troponin I will be elevated, the creatine kinase isozyme MB (CK-MB) will be increased, and a transient global or regional hypokinesis of the left ventricle and transient thickening of the left ventricle wall might be present on an echocardiogram (3).

However, it is important to keep in mind that exercise *per se* can increase the Troponin T levels. It has been indicated that up to 78% of runners who were investigated after a marathon had evidence of minor cardiomyocyte damage and that previous studies conducted indicated that these changes are likely to be physiological (34). It has been shown that the Troponin T level peaks 3 hours after exercise and returns to normal baseline levels within 24 hours (34). Furthermore, it has been documented that several studies have shown an increase in Troponin T and Troponin I levels in athletes following an endurance race (35). Despite exercise, there are also other conditions which might increase the Troponin levels. These include pulmonary embolism, myocardial infarction, sepsis, acute heart failure, amyloidosis and cardiac contusion (35).

It has been documented that several epidemiological studies have shown that myocarditis was the presumed cause of 5% of cases of sudden unexpected death precipitated by exercise in people under the age of 35 years (3). In 1979-1992, there was an increased rate of sudden unexpected death amongst

Swedish orienteers (16 people) and myocarditis was the most frequent histopathological feature. All of them had performed at or close to their maximum ability shortly before they died. Therefore, it has been suggested that a subclinical myocarditis can be aggravated by physical exertion (15).
It should be noted that sudden death due to myocarditis is rare and most cases of myocarditis resolve without residual symptoms (3). However, myocarditis can be associated with the development of an electrically unstable substrate resulting in ventricular tachyarrhythmias (33) and the postulated mechanism for sudden death of an athlete due to a viral myocarditis, is a fatal dysrhythmia (36).

According to the 36th Bethesda Conference held in 2005, athletes with probable or definite evidence of myocarditis should be withdrawn from all competitive sports for 6 months after the onset of clinical manifestations. If the left ventricular function, wall motion, cardiac dimensions, ECG, and serum markers of inflammation return to normal and there is no evidence of arrhythmias on Holter ECG monitoring, the athlete can resume training (33).

2.8.2. Myopericarditis

Myopericarditis is an inflammation of the myocardium and pericardium, and can present with an overlap of symptoms of myocarditis (as discussed above) and pericarditis (symptoms including sharp chest pain that is relieved with sitting forward and worsened by laying back) (4). The condition is most commonly caused by the group B Coxsackie virus, but can also be caused by the adenovirus, cytomegalovirus, influenza, echovirus, Epstein-Barr virus, herpes virus and parvovirus (4). During influenza, cardiac involvement usually occurs during the first week after the onset of symptoms, but there was a case report where myopericardial damage occurred on the 10th day after the onset of influenza symptoms (4).

The condition is usually self-limited, but it has been documented that strenuous exercise can markedly accelerate viral myopericarditis and enhance the inflammatory process (4).

2.8.3. Rhabdomyolysis

Rhabdomyolysis is the breakdown of skeletal muscle and can be as a result of a number of causes (discussed below). During this breakdown process, the integrity of the muscle membrane is compromised so that the contents of the muscle cell leak into the plasma. This may lead to the accumulation of free radicals and tumor necrosis factor-α (TNF-α) in the serum, which then leads to a systemic inflammatory reaction (4). The myoglobin released from the muscle cells is filtered through the kidneys and excreted into the urine. The myoglobin can be directly toxic to the renal tubule and can lead to acute renal failure (37). It should be noted that studies have shown that free radicals produced in any organ can induce myocardial damage (4). Pro-inflammatory cytokines, including TNF-α, are also considered important in the initiation of and development of the inflammatory cardiomyopathies and a s such, physicians should be aware that exertional rhabdomyolysis may lead to cardiac involvement (4).

There are numerous causes of rhabdomyolysis. These include exercise, infection, medications such as statins, alcohol and recreational drugs such as cocaine and amphetamine, myopathies and metabolic disorders such as hypothyroidism and diabetes mellitus (37).

Clinical features of rhabdomyolysis include acute muscle pain, limb weakness, swollen tender muscles, limb weakness, and contractures. Systemic symptoms might also be present, which include fever, nausea and vomiting, and tachycardia (37). Biochemical findings include an elevation in serum creatine kinase (CK) activity, white cell count, potassium, phosphate and urea and an

increase in the creatinine: BUN ration. There is a decrease in the calcium and albumin levels. Myoglobin is present in the urine (37).

It has been documented that the risk to develop rhabdomyolysis is increased when exercising during or after a viral illness (4). In one case report, a healthy 25-year-old-male presented with symptoms of rhabdomyolysis. The patient had a sore throat and cough 10 days prior to the onset of the rhabdomyolysis symptoms and influenza A was diagnosed with a rapid test. The patient was treated for 5 days with oseltamivir. The patient returned to physical activity 5 days after the symptoms had resolved. In this case, the patient also had myopericarditis, which could have been provoked by the rhabdomyolysis (due to the release of the free radicals), but further studies are required to confirm this (4). Clinicians treating patients with rhabdomyolysis should however be aware of the possible association with acute myopericarditis, especially in the presence of a recent influenza A infection.

In another case report, a healthy 36-year-old-male runner collapsed towards the end of a half-marathon. The patient's serum CK levels were 2 975 U/l (elevated) on admission to the hospital and peaked at 130 098 U/l, and a diagnosis of rhabdomyolysis was made. There was no recent history of an infection, but the patient did take a tablet containing ephedrine, which is an indirectly acting sympathomimetic amine and is structurally similar to amphetamine (38).

Treating physicians should therefore be aware that cold and flu medicine might contain ephedrine or pseudo-ephedrine, and athletes taking these medications might thus be at risk to develop rhabdomyolysis when they exercise, either due to the infection, or due to the medication.

2.8.4. Sudden death

It has been documented that a study of 78 sudden deaths during or immediately after exercise indicated that 5 of these individuals suffered from a recent URT infection (1). It has also been documented that there are numerous anecdotal reports of death in young healthy people who undertook strenuous exercise during viral illnesses (1).

2.8.5. Increased duration and severity of symptoms of an illness

There is conflicting evidence whether the duration of illness will be increased and the symptoms worsened if a patient exercise whilst suffering from an infection. It has been documented that exercising in the presence of an URT illness (with or without the presence of a fever), may aggravate the infection by causing more pronounced symptoms and/or prolong the length of the illness. The exercise may also trigger the development of a complication, such as a pneumonia or myocarditis ((2), (3)).

However, in randomised control trail, sedentary participants were followed to determine whether exercise affects the severity and duration of a naturally acquired URT illness. In this study it was shown that there was no difference between the cold symptom score mean values in the exercise and non-exercise groups. There was also no difference between the exercise and non-exercise groups in the mean number of days from baseline before the subjects were asymptomatic. The authors concluded that moderate exercise training in sedentary people during a naturally acquired URT illness will not affect illness symptom severity or duration (39). In summary, there are data that exercise whilst suffering from acute infections may affect the duration and severity of the illness, but more research is required in this field.

2.8.6. Other medical complications

It has been suggested that exercising with an acute infection, may result in cardiac dysrhythmias, particularly in the setting of an underlying undiagnosed heart condition, such as hypertrophic cardiomyopathy (HCM) (3). It is well established that exercise under normal circumstances can trigger a dysrhythmia in patients with HCM, but exercising with an underlying febrile infection may further increase the risk for the development of an dysrhythmia, as physical exertion in the presence of a fever can result in an increased hemodynamic load on the heart and precipitate dysrhythmias (3).

As discussed previously infections and fever can affect the nervous system, and lead to impairment of coordination. Exercising under these circumstances may increase the athlete's risk to damage a joint, ligaments or tendons, especially during sports that demand high precision (3).

Also as previously discussed, a fever affects the body's ability to regulate body temperature. This may lead to an increase in insensible fluid losses which might lead to dehydration, and an increase in the risk to develop heat stroke, especially if the exercise is performed in a hot and humid climate (2).

Finally, it has been documented that bronchial hyperreactivity may be triggered when an individual exercise during an ongoing URT infection (3).

2.8.7. Long-term medical complications: Post-viral fatigue syndrome

One of the most debilitating long term medical complications caused by a viral infection is post-viral fatigue syndrome (PVFS), which can persists for months (13), or years (1). This is one of the fatigue syndromes (others including chronic fatigue syndrome, fibromyalgia and neurasthenia) (40). PVFS usually occurs after a Coxsackie virus infection, but it can also present after infections caused by the influenza and varicella viruses (1), or an Epstein-Barr infection (41).

Symptoms of PVFS can vary widely and include lethargy, easy fatigability, myalgia (13), malaise and myalgia brought on by exertion, sore throat, sleep disturbance, loss of concentration, depression and/or anxiety (41), night sweats (12) and muscle weakness (40).
However, in one study the muscle strength and fatigability in a group of symptomatic patients were tested 3 months after the onset of a glandular fever-like illness. The results of this study showed normal strength and fatigability in the patients, and the subjective feeling of fatigue could not be explained by peripheral changes in muscle isometric force generation or fatigability (40).

2.8.9. Summary: Medical complications and risks associated with exercise training or competition in athletes with acute URT illness

It is well documented that there are numerous risks associated with exercising whilst suffering from an acute URT illness. Potential complications that can arise in the cardiovascular system include viral myocarditis (which will lead to no exercise for 6 months), myopericarditis and sudden death. Complications in the musculoskeletal system may also occur. Rhabdomyolysis is the breakdown of skeletal muscle and this may lead to acute renal failure. Fever can also affect the nervous system, which can lead to an impairment of coordination and this can lead to injuries of the joints, ligament and tendons. Other potential complications include bronchial hyper-reactivity, an increase in the duration and severity of the illness, heatstroke and long-term complications such as post-viral-fatigue syndrome. A summary of the medical complications and risks associated with exercise whilst suffering from an acute URT illness is depicted in Table 2.8.

Table 2.8. Medical complications and risks associated with exercise training in athletes with an acute URT illness

System	Complication
Cardiovascular	Viral myocarditis Myopericarditis Dysrhythmias Sudden death
Musculoskeletal	Rhabdomyolysis with or without acute renal failure Joint, ligament and tendon injuries due to impaired motor coordination
Respiratory system	Bronchial hyper-reactivity
Others	Post-viral fatigue syndrome Increased duration and severity of symptoms of illness Heatstroke

2.9. Return-to-play (RTP) guidelines for athletes with acute URT illness

Acute URT illness is the most common medical illness that a team physician encounters ((1), (5), (6), (7)). Therefore, the most common clinical decision a physician, who is responsible for the medical care of athletes, makes, is when an athlete can safely return to training or competition.

This important clinical decision has been highlighted more than 30 years ago in a case report published in the Lancet in 1982. In this case report, two athletes are described. Both athletes presented with symptoms of influenza but opted to exercise within a week from the beginning of the symptoms of infection. Both athletes suffered from bacterial meningitis and one of the athletes died (29).

Most guidelines recommend that the athlete can safely resume regular training a few days after the resolution of symptoms if the athlete had symptoms of a common cold only, and symptoms of systemic involvement was absent. If, however, there were symptoms or signs of systemic involvement (fever,

tachycardia, swollen lymph nodes, extreme tiredness, and myalgia), intensive training should be postponed for 2 to 4 weeks ((12), (15)).

Other recommendations are more specific. It has been suggested that rest should be advised to an athlete with an infection when fever is present (>38°Celcius (C)), or when the individual's resting temperature has increased by 0.5 to 1°C or more and their resting pulse rate has increased by 10 beats per minute or more in combination with symptoms such as malaise, myalgia, arthralgia or headache (3). An acute onset of general malaise, especially in combination with pains in the muscles or joints, should also prompt the recommendation of rest, even in the absence of a fever (3). In most cases, if a fever is present, rest should be recommended until the fever has abated. Training can then be gradually resumed and if any symptoms referable to the heart appear (chest pain, chest discomfort, irregular heartbeat, abnormal breathlessness, abnormal fatigue or exertional syncope), the exercise bout should be stopped immediately (3). As these could be the symptoms of a myocarditis, a physician should be consulted. When specific symptoms and signs are taken into consideration, athletes with a *runny nose* without a sore throat, cough or systemic symptoms and signs, rest should be advised for 3 days, after which training can gradually be resumed if the symptoms does not become intensified (3). In the athlete with a *sore throat* without any other symptoms, especially systemic symptoms, caution is advised until the sore throat starts to improve. If the infection was however caused by a β-haemolytic streptococcal bacteria, the athlete should rest until the sore throat has resolved completely, as myocarditis may follow the infection (3). Athletes with *gastroenteritis* should avoid physical activity, while exercise should be avoided when a *cystitis* is present until all the symptoms have resolved (3).

To date, the most widely used clinical guideline to determine RTP following an acute URT illness is the "neck check" (2). This guideline states that if an athlete has *symptoms confined to "above the neck"*, such as a *runny nose, sore throat,*

sneezing or nasal congestion, the athlete can be allowed to exercise if he or she should feel comfortable doing so. Exercise should be attempted at mild to moderate intensity for 10-15 min. If the symptoms worsen, the exercise should be stopped and the athlete should rest. If, however, the symptoms do not worsen, participation should be allowed. If the athlete however has *systemic symptoms* such as *fever, swollen lymph nodes, myalgia, coughing, diarrhoea or an elevated heart rate*, rest should be advised for a period of 7-14 days until the symptoms have resolved, due to the risk of serious complications. Once the infection had resolved, the athlete should ease back into training, taking one to two days for every training day missed to build back up to pre-illness levels.

In summary, current recommendations for contraindications to exercise participation in athletes with an acute URT illness are: (8)

- Presence of fever
- Presence of myalgia (muscle pain)
- Presence of chest pain
- Resting tachycardia
- Excessive shortness of breath
- Excessive fatigue
- Swollen painful lymphadenopathy

It is important to note that certain infections, such as infectious mononucleosis (IM) require additional special considerations, as the infection causes an enlarged spleen due to lymphocyte infiltration. The enlarged spleen has disrupted architecture and this makes it fragile (2). The spleen can rupture if it is subjected to a blow or increased pressure (3). Data indicate that 50% of splenic ruptures occur without a direct blow to the spleen and the risk of rupture is 0.1-0.5% (8). The risk for rupture is highest in the first 3 weeks, but is very rare after 28 days (2).

In additional to the general guidelines previously mentioned, athletes with IM with splenomegaly should refrain from doing sport for at least 3 weeks. After the 3-week period, the athlete may resume low-impact, non-contact training at 50% of pre-illness level if there is resolution of symptoms (fever, fatigue, sore throat and lymphadenopathy), normalisation of laboratory markers and resolution of splenomegaly. If there is no relapse of symptoms and athlete continues to improve in the first week of graded return to exercise, full sport participation, including contact sport, may be allowed (2). Full fitness is very often only reached after 3 months of training (8). It is important to note that the size of the spleen should be evaluated by an ultrasound, as a physical examination of the spleen is unreliable to detect splenomegaly (2).

In summary, it has been well documented that acute URT illnesses are the most common medical problem an exercise and sport medicine physician will encounter. As there are many possible medical complications that can develop when an athlete participate in sport when an URT illness is present, physicians utilize a clinical guideline called the “neck check” to decide whether an athlete is eligible to participate in an exercise session whilst having an URT illness. The guideline stipulates that an athlete can participate in sport when symptoms and signs are local (blocked nose, runny nose, sore throat, erythematous throat) and symptoms and signs of systemic involvement (fever, tachycardia or resting heart rate increase by 10 beats or more, myalgia, malaise, lymphadenopathy, cough, chest pain and shortness of breath) is absent. If systemic symptoms are present, rest should be advised for 7 to 14 days. If the athlete “pass the neck check” and are allowed to exercise, or when the athlete returns from an illness, exercise should be resumed at moderate intensity for 10-15 minutes. If any symptoms return or are worsened by the exercise, the exercise session should be stopped and further rest should be advised.

Special considerations are required for a few conditions. Firstly, no exercise should be allowed when the athlete has cystitis or gastroenteritis. Secondly,

when an athlete has infectious mononucleosis, non-contact sport should only be considered after 3 weeks and contact sport after 4 weeks of rest, as the enlarged spleen is at risk to rupture within this time frame. The athlete may only participate in sport once symptoms have abated and the spleen has regressed to its normal size (proven by sonography). Exercise should be resumed at 50% of the pre-illness level of intensity and volume for 1 week. If the athlete continues to improve, full training may be resumed.

2.10. Prevention of acute illness in athletes

2.10.1. Introduction

Athletes often lose weeks of training each year due to acute illnesses, of which URT illness is the most common. An athlete may also miss that all-important race for which months of preparation has gone into, due to an URT illness. It is for this reason that prevention of illness is of utmost importance. The following preventative measures will be briefly reviewed in this section:

- Personal hygiene
- Nutritional strategies
- Probiotics
- Other strategies.

2.10.2. Personal hygiene

Personal hygiene is not only the most important, but also the most practical and easiest preventative strategy. Most URT infections are transmitted through airborne droplets (sneezing and coughing) and by contact (direct skin contact or indirect contact with sporting equipment) (3). As such, there are preventative measures that can reduce transmission.

The most important preventative measure is frequent hand washing ((1), (2), (27)), and avoiding contact between the hands, eyes and nose, as this is a primary route of introducing viruses into the body (12). Other measures include covering the mouth and nose with the cubital fossa when sneezing or coughing (27), avoiding direct skin-to-skin contact (1), and avoiding contact with ill individuals ((2), (12)). Sharing of water bottles, towels and sporting equipment should be strongly discouraged ((1), (2)).

In summary, the following personal hygiene strategies should be followed to prevent an URT illness:

- Avoid contact with people who are ill
- Wash hands frequently
- Avoid putting hands to eyes and nose
- Do not share water bottles, towels or sporting equipment
- Avoid skin-to-skin contact

2.10.3. Nutritional strategies

Nutrition is an important preventative measure. Various nutritional components will be briefly reviewed in this section, including vitamins, glutamine, cysteine and theanine, and CHO ingestion during exercise

2.10.3.1. Vitamins

Vitamin C

It has been shown that vitamin C supplementation may reduce the risk of symptoms of acute URT illness in distance runners. In one double-blind, placebo controlled study that was conducted on 92 runners who had entered the 1990 90km Comrades Ultra-Marathon in South Africa, daily supplementation with 600mg vitamin C reduced the incidence of post-race URT illness, from 68% to

33% ($p<0.01$) (42). A limitation to this study is that the URT illnesses were never proven to be infectious. Furthermore, whether vitamin C supplementation reduces the risk of acute illness during training or in the pre-race period has not been studied.

Vitamin D

In one prospective cohort study, the influence of vitamin D status on the incidence of respiratory illness and immune function during a 4 month (16 week) winter training period in endurance sport athletes was examined (43). In this study, 225 participants were divided into a vitamin D deficient group (plasma 25(OH)D < 30nmol/L), an inadequate vitamin D group (plasma 25(OH)D 30-50nmol/L) and an optimal vitamin D group (plasma 25(OH)D > 120nmol/L). The results of this study showed that, after 16 weeks, a significantly higher proportion of participants presented with symptoms of an URT illness in the vitamin D deficient group compared with the optimal vitamin D group (deficient group 67%, optimal 27%; P=0.039). The total number of URT illness symptom days (optimal 5, deficient 13; P=0.059) and the median symptom-severity score (optimal 43, deficient 102; P=0.013) in the vitamin D deficient group was also significantly higher than in the other groups. Finally, saliva secretory immunoglobulin A (SIgA) secretion rate in the optimal vitamin D status group was also significantly higher than the other groups (optimal 38.7µg/min, inadequate 19.5µg/min, deficient 23.6µg/min; P=0.018).

This study indicated that vitamin D status could influence URT illness symptom incidence, the duration of an illness episode and the severity of symptoms. An optimal vitamin D level has more favourable outcome by lowering the incidence, shortening the episode and reducing the severity. The study also indicated that an optimal vitamin D level increased the secretion rate of salivary IgA, which functions as a first line of defence against pathogen invasion. It is known that there is an inverse relationship between salivary IgA values and URT illness

prevalence and as such, vitamin D supplementation might enhance the prevention of an URT illness in athletes.

2.10.3.2. Glutamine

Glutamine is a naturally occurring non-essential neutral amino acid and is the most abundant free amino acid in human muscle and plasma (44). It is an important fuel for the immune system, as lymphocytes and macrophages utilise glutamine at high rates and are dependent on glutamine for replication.
It was postulated than when plasma glutamine concentration decreases below a physiologically normal range (0.5-0.9Mm), limited glutamine availability may impair certain immune cell functions and increase an individual's susceptibility to infections such as URT infections (45).

It has been suggested that a reduction in plasma glutamine concentration, associated with period of heavy training, could be partly responsible for immune suppression in endurance athletes and that immune function could be impaired by the reduction intramuscular and plasma concentrations of glutamine, associated with prolonged exercise (44).

It was postulated that oral supplementation with glutamine should prevent the fall in plasma glutamine concentration after exercise and thus prevent the associated post-exercise immune impairment, if the reduction in plasma glutamine concentration indeed was a causal factor in the transient post-exercise depression in immune function (44). However, several glutamine supplementation intervention studies showed that glutamine supplementation before and after exercise has no detectable effect on exercise-induced changes in immune cell functions (44). It was documented that in one randomized, cross-over, placebo-controlled study, participants performed 3 consecutive bouts of cycle ergometer exercise at 75% VO_{2max} for 60, 45 and 30 minutes with 2 hours rest in between each bout (44). The participants ingested 0.1g/kg body mass

glutamine 30 minutes before the end of each exercise bout and 30 minutes after each exercise bout. Although the glutamine supplementation prevented the reduction in the plasma glutamine concentration, it did not prevent the reduction in lymphocyte proliferation or the decrease in NK-cell activity.

It has been documented in a review that an acute exercise bout and intense training cause a reduction in salivary IgA concentrations (8). The levels return to the normal range within 1 hour after cessation of the exercise. However, maximal exercise bouts may prolong the return to normal values and repetitive exercise bouts during periods of heavy training may result in a cumulative reduction in salivary IgA concentrations which can predispose the athlete to URT infections (8). Intense exercise may induce small transient decrements in plasma glutamine concentrations, which results in a reduction of glutamine supply to the mucosal tissues secondary to a decrease in glutamine availability. Repetitive reductions in glutamine supply to IgA-producing lymphoid cells could affect their ability to produce IgA and this can lead to an increased susceptibility to infection (45).

Theoretically, chronic glutamine supplementation would help maintain glutamine homeostasis and secretory IgA (sIgA) concentration. However, in one study conducted on 13 healthy runners, it was documented that chronic, high-dose glutamine supplementation during 9 days of interval training had no effect on salivary IgA concentration or output. It did however resulted in a higher nasal IgA during training (of which the biological significance is uncertain) (45).

In summary, the available evidence is thus not strong enough to warrant a recommendation for an athlete to use a glutamine supplement to prevent URT illness. It should be noted though that there are some suggestions of a possible role for glutamine in stimulating anabolic processes, including muscle glycogen and protein synthesis (44).

2.10.3.3. Cystine and Theanine

Cystine is a dipeptide of cysteine and a precursor of glutathione, which is responsible for the anti-oxidative response inside the body. Theanine is an amino acid that is metabolised to glutamic acid and ethylamine within the intestinal tract, liver and kidneys. One study reported that oral administration of cystine and theanine improved antibody production in the elderly, and this lead to a randomised, double-blind, placebo-controlled, parallel-group study in 15 male long-distance runners (46). Eight participants were assigned to a cystine/theanine group who ingested 700mg of cystine and 280mg of theanine per day for 10 days prior to a summer training camp. The athletes ran an average of 15.2 km/day in the 10-day period prior to the camp and 18.1 km/day during the 11-day training camp. The study showed that ingestion of cystine and theanine prevented a reduction in the leucocyte count after the training camp (which was observed in placebo group), and prevented an increase in the neutrophil count and high sensitive CRP after the camp (which was also observed in the placebo group). The study thus suggests that oral supplementation with cystine and theanine prevented changes in the inflammatory responses after prolonged, intense endurance exercise, as well as preventing lowering of the immune function, and contributed to the prevention of infection as well as reducing their symptoms.

2.10.3.4. Carbohydrate ingestion during exercise

It has been documented that CHO ingestion by endurance athletes during intensive exercise is associated with an attenuated cortisol, growth hormone, and epinephrine response, fewer perturbations in blood immune cell counts, lower granulocyte and monocyte phagocytosis and oxidative burst activity, and a diminished pro- and anti-inflammatory cytokine response compared to placebo ingestion (47). In a review of 66 placebo-controlled and/or crossover trials, it was evident that the consumption of ≥ 6% CHO (1 litre per hour) during prolonged

exercise was an effective approach to maintain immune function in athletes. This might be due to the attenuating effects on the exercise-induced increases in total leukocyte counts and/or leukocyte subsets such as monocytes and neutrophils. The ingestion of ≥ 6% CHO also attenuates cytokine changes in response to prolonged exercise, in particular interleukin 6 and 10, and maintains blood glucose levels, which leads to an attenuated post-exercise cortisol level, resulting in a less suppressed immune function (21). There was however no mention in the review that the maintenance of the immune function translates into a reduction in URT illness symptoms.

In conclusion, there is some evidence that ingestion of ≥ 6% CHO during prolonged exercise can maintain the immune function, but more research is required to prove that this translate into the reduction of URT illness.

2.10.4. Probiotics

There is increasing evidence from a double-blind, randomised controlled trial and meta-analysis of randomised, placebo-controlled trials that probiotic supplementation can reduce the number, duration and severity of acute infectious diarrhoea and URT infection in the general population (48). Furthermore, it has been documented that probiotics may reduce gastrointestinal illness in endurance athletes (48). Recently, there are some data from a double-blind, placebo-controlled, crossover trail that indicate that probiotic supplementation (Lactobacillus fermentum VRI-003) (PCC) might be useful for reducing the duration of URT infections and the severity of the respiratory illness in elite athletes (49).

In a randomised, double-blind, placebo-controlled study 88 healthy, physically active participants were included in a study to determine the effects of supplementation with *Lactobacillus fermentum* (PCC®) on URT infections and gastrointestinal symptoms over a 15-weeks winter training period (48). The

participants were divided into either a probiotic or placebo treatment group and consumed a capsule on a daily basis. The participants recorded gastrointestinal, URT and lower respiratory tract symptoms on a daily basis on an illness-log for the duration of the study (15 weeks). Two or more symptoms on 2 consecutive days were defined as an illness period.

The study showed a 2-fold increase in the number and duration of mild (low-grade) self-reported gastrointestinal symptoms in both male and females taking the probiotic. However, in the male participants, the self-reported severity score of gastrointestinal illness was lower compared to the males in the placebo group and this positive effect increased with higher training loads.
The effects of the probiotic supplementation on URT illness was however unclear in both male and females. In the male participants taking the probiotic, the number, duration and severity of lower respiratory tract infections were 50% lower compared to the males in the placebo group. However, in female participants in the probiotic group, there was a 2-fold increase in the number and duration of lower respiratory tract infections compared to the participants in the placebo group, but the severity was reduced.

In conclusion, there is good evidence that that probiotic supplementation can reduce the number, duration and severity of acute infectious diarrhoea and URT infection in the general population. However, some conflicting evidence exists pertaining to the effect a probiotic may have on elite and endurance athletes. Some data indicate that probiotics may reduce the duration of URT infections and the severity of the respiratory illness in elite athletes and probiotics may reduce gastrointestinal illness in endurance athletes. Other data indicate that probiotics only decreased the severity of gastrointestinal illness in male athletes (not the number of episodes), decreased lower respiratory tract illness episodes and severity in male athletes only, and the effect on URT illness in male and female athletes was unclear. More research is necessary in this field.

2.10.5. Other preventative strategies

Other preventative strategies that are aimed at reducing the risk factors associated with an increased incidence of URT illness include the following:

- Eating a well-balanced diet is important, as inadequate nutrition may contribute to impaired immunity because normal function of the immune cells requires an adequate amount of water, electrolytes, glucose and proteins ((1), (2), (8), (12), (21)).
- Rapid weight loss (more than 1% of body weight per week) should be avoided, as it has been linked to negative immune changes, especially T-cell suppression (12).
- Sleep disruption has also been linked to immune depression (12). An effort should thus be made to get adequate sleep ((1), (2), (8)).
- There are many reports of URT illness resulting from increased training, and also in overreached and overtraining syndrome athletes (24). It is thus important to avoid overtraining and fatigue ((1), (2), (8), (12)).
- A single session of strenuous endurance exercise is followed by temporary functional immunodepression (as discussed in section 2.4.1.1). If resting periods between such exercise sessions/ competitions are not long enough to allow the immune function to recover, the athlete is at an increased risk of becoming ill. It is thus important to space high intensity and prolonged exercise sessions and races as far apart as possible ((1), (2), (3), (8)).
- Mental stress has been linked to an increased risk for URT illness (12). It is thus important to reduce life stressors ((1), (2)).
- Vaccinations are available to prevent illness caused by influenza viruses and it is strongly recommended to obtain these during the winter months ((1), (2), (3), (12), (27)), as the influenza vaccinations can reduce respiratory illness by 30-50% (27).

2.10.6 Summary: Preventative strategies

Numerous preventative strategies have been proposed in an attempt to reduce the incidence of URT illness and gastrointestinal disorders in endurance athletes. Personal hygiene is by far the most important strategy. Nutrition has been proposed as a possible measure to prevent illness. *Vitamin C* supplementation was proven to prevent post-race illness, but further research is required to investigate its potential to prevent pre-race illness. It has been recognized that *vitamin D* plays an important role in upregulating immunity (43) and it has been shown that vitamin D supplementation might enhance the prevention of an UTR infection in athletes. *Glutamine* is an important fuel for the immune system and it has been postulated that prolonged exercise is associated with a decrease in intramuscular and plasma concentrations of glutamine. However, the currant available evidence is not strong enough to warrant a recommendation of glutamine supplementation to prevent URT infections in athletes. There is some evidence that *cystine and theanine* supplementation prevents changes in the inflammatory response associated with prolonged, intense endurance exercise, and prevents lowering of the immune function. Supplementation was proven to contribute to the prevention of infection as well as reducing their symptoms in endurance athletes. There is some evidence that the consumption of ≥ 6% CHO (1 litre / hour) during prolonged exercise results in a less suppressed immune function. However, more research is required to prove that this translate into the reduction of URT illness. Probiotics have been studied as a possible preventative measure for URT illness in athletes. Conflicting evidence exist, as some data indicate that probiotics may reduce the duration of URT infections and the severity of the respiratory illness in elite athletes and probiotics may reduce gastrointestinal illness in endurance athletes. Other data indicate that probiotics only decreased the severity of gastrointestinal illness in male athletes (not the amount of episodes), decreased lower respiratory tract illness episodes and severity in male athletes only, and the effect on URT illness in male and female athletes was unclear. More research is necessary in this field. Other preventative

strategies include eating a well-balanced diet, avoiding rapid weight loss, getting adequate sleep, avoiding overtraining and fatigue, reducing life stressors and spacing high intensity and prolonged exercise session and races as far apart as possible.

2.11. Summary: Acute illness in athletes with specific reference to acute pre-race illness in distance runners

- Epidemiological data indicate that endurance athletes undergoing intense and prolonged training are at increased risk for URT illness.
- However, there are little data on the incidence of URT illness in runners prior to an endurance race, but in two studies at marathons this appears to be high (between 17% and 40%) ((14), (18)).
- Most data on the incidence of URT illness in runners are based on self-reported questionnaires and there is no evidence that these URT illnesses were in fact due to infection.
- Other conditions such as allergic rhinitis, asthma, thyroiditis, and gastro-oesophageal reflux as causes of symptoms of URT illness should be considered.
- More research to determine the incidence of a clinically diagnosed URT infection in runners (prior to and after an endurance race) is required.
- The relationship between the “dose of exercise” and the risk of URT illness symptoms is a “J-shaped” curve.
- Individuals who exercise at moderate intensity and duration having the smallest risk to develop an URT illness, while sedentary individuals have a higher risk to develop an URT illness.
- Endurance athletes training at high intensity and prolonged duration have the highest risk to develop an URT illness (8).
- There are a number of changes in immune system parameters after an acute exercise bout and these last for 3-72 hours.

- ❖ This is known as the “open window” period and may be associated with an increased risk of susceptibility to illness.
- ❖ Numerous risk factors to develop an URT illness in distance runners have been identified.
- ❖ Intrinsic risk factors include exercising after a recent URT infection, low sIgA, BMI > 75th percentile and being a female.
- ❖ Extrinsic risk factors include a training distance > 65km/week, training at intensities > 50-75% of maximum ability, training duration > 90 min per session, inadequate recovery time between heavy exercise bouts, stress, fatigue, inadequate sleep, inadequate calorie and CHO intake and exercising without food and in a dehydrated state.
- ❖ Infections, including URT infections, have a detrimental effect on several systems in the body, including the cardiovascular, neurological, muscular, thermoregulatory and metabolic systems.
- ❖ Exercising whilst suffering from an URT infection can be associated with a number of medical complications.
- ❖ These complications include myocarditis, myopericarditis, rhabdomyolysis, post-viral-fatigue syndrome, dysrhythmia, heat stroke, bronchial hypersensitivity and even sudden death.
- ❖ Currently, advice whether an athlete can participate in sport whilst being ill, is based on a clinical guideline known as the “neck check”.
- ❖ However, there are very few studies in the literature to validate this guideline.
- ❖ Currant return-to-play (RTP) guidelines can be summarized as follows:
    - In all infections, rest should be advised for the first 3 days, as the symptoms might be part of a prodromal phase of a more sinister infection, such as a meningitis or rubella.
    - If the athlete experienced symptoms, which would have passed the “neck check”, i.e. local symptoms/signs are present and systemic symptoms/signs are absent, exercise should be allowed when the

athlete feels comfortable doing so. Exercise should however be attempted at 50% intensity for 10-15 minutes and if symptoms worsen or if symptoms referable to the heart appear (chest pain, chest discomfort, irregular heartbeat, abnormal breathlessness, abnormal fatigue or exertional syncope), the exercise bout should be stopped immediately and further rest should be advised.

- If a sore throat is present and a β-haemolytic streptococcal bacteria is suspected, rest should be advised until the symptom has subsided completely, as myocarditis may follow a sore throat caused by a β-haemolytic streptococcal bacteria.
- If systemic symptoms are present, rest should be advised for 7-14 days and once the infection had resolved, the athlete should resumed exercise at mild to moderate intensity for 10-15 min. If symptoms worsen or if symptoms referable to the heart appear (chest pain, chest discomfort, irregular heartbeat, abnormal breathlessness, abnormal fatigue or exertional syncope), the exercise bout should be stopped immediately and further rest should be advised.
- Contraindications to exercise participation in athletes with an URT illness fever, resting tachycardia (or pulse rate which has increased by ≥ 10 beats / min, myalgia (muscle pain), swollen painful lymph glands, coughing, shortness of breath, excessive fatigue, and chest pain.

❖ RTP guidelines in athletes with infectious mononucleosis require special consideration, as there is an increased risk for spontaneous splenic rupture during the first 3 weeks of the illness. Non-contact sport is allowed after 3 weeks of rest. Training should be commenced at 50% of the training load prior to the illness and full fitness is only expected after 3 months. Contact sport may only be resumed after 4 weeks of rest and after splenomegaly was excluded by an ultrasound (8).

- Strategies to prevent URT illness have been proposed and include the following: personal hygiene (hand washing, avoiding ill people, avoid sharing water bottles and sporting equipment, avoid skin-to-skin contact, avoid putting hands to eyes and nose), nutritional strategies (vitamin C and D supplementation, glutamine supplementation, cystine and theanine supplementation, and adequate CHO intake during prolonged training sessions), probiotics supplementation, and other preventative strategies (including eating a well-balanced diet, avoiding rapid weight loss, avoiding overtraining and fatigue, getting adequate sleep, spacing of heavy exercise sessions as far apart as possible, immunization, decreasing of life stressors).
- In conclusion, very little data is available in the literature to validate the clinical guidelines that are used by physicians, and applied by athletes, in an attempt to minimize the possible medical complications when exercising with an infection or illness.
- More studies need to be conducted to determine if current guidelines are adhered to, and if information given to athletes can alter their decision to participate in competition and training.

Chapter 3

An acute pre-race illness screening and educational intervention program effectively reduces the number of runners starting a race, thereby preventing any increased risk of not finishing the race, or risk of developing of medical complications

3.1. Introduction

It has been well established that the most common acute illnesses affecting athletes are upper respiratory tract (URT) illnesses, followed by gastrointestinal diseases and skin disorders ((1), (5), (6), (7)). It has been documented that an athlete is at an increased risk to develop an upper respiratory tract illness during periods of high intensity (about 75% -80% of maximum ability) and prolonged (> 60min) training sessions (8). High intensity and prolonged duration training sessions are associated with a decreased immunity, which can last 3 to 72 hours. This period is referred to as the “open window” period and it is during this period that the athlete is particularly vulnerable to contract an illness ((3), (8), (12), (13) (21)).

There are also data suggesting that athletes, participating in endurance events, such as marathons and ultra-marathons, have an increased risk of developing an URT illness in the period after the event ((2), (8), (12), (13), (14)). It has been shown that a runner has a 100-500% increased risk to develop an URT illness after an ultra-marathon (16). Runners with a high training load (>65km per week) (8), fast marathon time ((8), (17)) and those who had a recent pre-race illness (18), have the highest risk of developing a post-race URT illness.

However, data on the prevalence of an acute illness in the immediate pre-race period are limited and vary. One study indicated that 17% of runners participating

in the 2000 Stockholm Marathon had an illness episode in the 3 weeks prior to the race (18). Another study indicated that 40% of runners participating in the 1987 Los Angeles Marathon reported an URT illness in the 8 weeks prior to the marathon (14). Although limited, these data therefore indicate that a significant number of runners have symptoms of an acute illness in the period immediately before a race, and these are mostly respiratory tract illnesses.

The effects of an acute illness on exercise performance and the possible medical complications when exercising with an illness, particularly if the illness is as a result of an acute infection have been reviewed in Chapter 3 (Sections 2.7. and 2.8. respectively). These complications can be life threatening and have been associated with an increased risk of sudden death due to myocarditis (3).

One of the most common clinical decisions for the sport and exercise medicine physician is the return-to-play following an acute illness. Currently, clinicians use a clinical tool, the “neck check”, to asses and then advise an athlete with an acute illness to either participate in an event (or exercise session) or not (9). According to this clinical guideline athletes are advised not to participate if there are any systemic symptoms (fever, myalgia, chest pain, resting tachycardia, excessive shortness of breath, excessive fatigue, or swollen painful lymphadenopathy). This guideline does allow participation at lower exercise intensity, with ongoing monitoring of symptoms, if athletes suffer only from “localized” URT symptoms (runny nose, blocked nose, sore throat).

However, as far as we could ascertain, there are currently no studies to validate the “neck check” clinical guideline. More specifically, it is not clear 1) what the prevalence of athletes with symptoms of an acute illness is in the 1 week-period prior to an endurance race, 2) how many athletes would adhere to advice given by their medical doctor using the “neck check” symptom guideline, 3) whether athletes with symptoms of an acute illness prior to the race, and then continue to

participate in the race either are not able to complete a race, or suffer from any medical complications during or immediately after the race.

3.2. Aim of the study

The aim of this study was to determine 1) the period prevalence of runners with symptoms of an acute illness one week prior to the 2012 Two Oceans endurance running races (21km and 56km), 2) the period prevalence of runners who “fail” the “neck check” and therefore would be advised not to participate in the race, 3) the incidence of runners with symptoms of an acute illness (and who then received educational material) that did not start the race, 4) the incidence of runners with symptoms of an acute illness (and who then received educational material) that started, but not finish the race, and 5) the incidence of runners with symptoms of an acute illness (and who then received educational material) that started, but develop medical complications during the race.

3.3. Methods

3.3.1. Type of study

This was a prospective cohort study.

3.3.2. Selection of participants

Prior to the onset of the study, the Research Ethics Committee of the Faculty of Health Science at the University of Cape Town approved the protocol (HREC REF: 009/2011) (Appendix C). All the athletes (n=25455) who entered the 2012 Old Mutual Two Oceans ultra-marathon (56km) and half-marathon (21km) in Cape Town, South Africa, were regarded as potential participants for the study.

All the potential participants were informed about the study, which was part of a larger study on reducing medical complications during running. All runners who entered for the Two Oceans half-marathon and ultra-marathon races (n=25455) and who gave informed consent to receive further email communication were contacted in the 5 days prior to the race. All these runners received information and a pre-race acute illness questionnaire to complete (Appendix A).

However, as not all runners had access to email during the pre-race period, an additional opportunity was created for these runners to complete the pre-race acute illness questionnaire at the registration expo during the 3-day period prior to the race. At the time of the pre-race expo that was held during the 3-day pre-race period, runners who gave verbal consent could also complete a pre-race acute illness questionnaire during interviews by medical staff of the research team. These interviews were held while runners were finalizing their registration for the race. Samsung electronic tablets were used to log the answers and the data was submitted electronically and added to the database from the responses that were received via the email.

Of the total number of runners registered for either 56km or 21km race (n=25455), a total of 7992 runners completed the pre-race acute illness questionnaire (6907 through email communication, and 1085 during pre-race interviews). Of the 6907 runners who completed the questionnaire by email, 5954 completed the registration process and could run in the race. Therefore, the final cohort of runners who completed the pre-race acute illness questionnaire for this study was 7035 (5954 by email, and 1085 by interviews). The cohort of runners therefore represented 27.6% of all the race entrants (7035/25445).

3.3.3. Pre-race acute illness questionnaire

The pre-race acute illness questionnaire (Appendix A) was preceded by a paragraph explaining the importance of acute illness prior to a race. This was

followed by a brief description of any possible symptoms of an acute infective illness as follows:

> *"The symptoms of infections vary but include the following: generally not feeling well, fever, general muscle pain, general joint pain, general tiredness, headache, sore throat, blocked or runny nose, sore ears, cough, wheeze, diarrhoea, nausea, vomiting, or abdominal pain".*

This description was then followed by a single question to ascertain whether the runner experienced any symptoms of an acute illness in the 7-day period prior to the race as follows:

> *Do you have any of these symptoms of acute illness (today or in the last 7 days)? Yes No*

If a runner selected the "No" option they were notified "to enjoy the race". If they selected the "Yes" option, additional choices were given. Runners were asked to select (one or more) symptoms they experienced form a list. These symptoms were as follows: systemic symptoms (fever; cough; general muscle pain), respiratory symptoms (sore throat; runny nose; blocked nose), gastrointestinal symptoms (nausea; vomiting; diarrhoea; abdominal pain), bladder infection, skin rash and other symptoms. Once they indicated which symptoms they experienced, an automated email was sent to them with an information leaflet attached to it.

3.3.4. Educational intervention

Runners who indicated that they experienced symptoms of an acute illness were given educational information (Appendix B) with general information about acute illness, information about the risk to exercise with the illness, and specific guidelines on when not to participate while certain symptoms are present. Runners with symptoms received one of three leaflets, depending on the symptoms runners listed in their responses: 1) specific advice on respiratory tract

infections and running, 2) specific advice on gastro-intestinal illness and running, or 3) general advice on acute infections and running for non-specific infective symptoms (Appendix B). The information leaflets were distributed by an automated email system (for the email communication) or given as a hand-out (following the interview).

3.3.5. Runner follow-up on race day

All the runners were followed during race day. Information about each runner was obtained from a database of the race organizers. Data obtained related to runners who actually started the race and which of the athletes who started the race, finished the race. These data was obtainable because each runner was required to wear an electronic chip ("Champion" chip) that was strapped to their running shoes which contains information about the runner. These chips activated a signal when the athletes passed over a mat as they crossed the starting line and finish line. A runner was considered to be a "non-starter" if the start-line mats did not capture a start time on race day. Similarly, a runner was considered a "non-finisher" if the finish-line mats did not capture a finish time on race day.

Data were also obtained from the medical stations on route and the medical tent at the finish line. Runners who developed any medical complication during the race were treated at these facilities. However, all runners who voluntarily withdrew from the race did not necessarily report to the medical facilities. Each runner who was admitted to the medical facilities was scanned (their race number was obtained) at the entrance to the facility and each runner was scanned out again as they left the medical facility. Their final diagnosis (ICD-10 code) was logged electronically against their race numbers on Samsung electronic tablets. All runners who were treated at a medical facility were considered to have a medical complication.

3.3.6. Measures of outcome

The main measures of outcome of the study were as follows:

- The period prevalence (%) of runners with symptoms of an acute illness in the 7-days prior to an endurance race
- The did-not-start (DNS) rate (% runners) in runners in different groups
- The did-not-finish (DNF) rate (% runners) in runners in different groups
- The medical complication (MC) rate (% runners) in runners in different groups

3.3.7. Analysis of data and sub-groups

As previously indicated, runners could select one or more symptoms of acute illness in the illness questionnaire (Appendix A). Based on the response to the pre-race acute illness questionnaire, runners were firstly categorized into an asymptomatic control group (n=5697) (81% runners), and a symptomatic group (including all the runners with any symptoms of an illness) (n=1338; 19%).

Runners in the symptomatic group were further divided into sub-groups as follows: systemic symptoms group (n=530), respiratory symptoms group (n=896), gastrointestinal symptoms group (n=249) and runners who failed the “neck check” (n=878).

3.3.8. Statistical analysis of data

All data were entered into an Excel spread sheet (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. Period prevalence (%) of runners with symptoms of an acute illness in the 7-days prior to an endurance race

Of the 7035 runners, 5697 runners (80.89%) reported no symptoms in the 7 days prior to the race, while 1138 runners (19.02%) did experience symptoms of an acute illness in the 7-day period prior to the race. The frequencies of the symptoms experienced by the athletes can be viewed in Table 3.1. The most common symptom experienced by the runners was a sore throat (34.5%), followed by a runny nose (29.9%), general tiredness (27.8%), a blocked nose (23.3%) and headaches (22.6%). Runners were allowed to report more than one symptom.

Table 3.1. Frequencies of symptoms experienced by runners one week prior to an endurance race

Symptom Experienced	Number of athletes	Percentage (of 1338 athletes)
Sore throat	452	34.5%
Runny nose	392	29.9%
General tiredness	365	27.8%
Blocked nose	305	23.3%
Headache	296	22.6%
General muscle pains	282	21.5%
Cough	243	18.5%
diarrhoea	154	11.7%
General joint pains	149	11.4%
Fever	105	8%
Sore throat	98	7.5%
Abdominal pain	98	7.5%
Nausea	65	5%
Wheezing	48	3.7%
Bladder infection	40	3.1%
Skin rash	16	1.2%
Vomiting	15	1.1%

When these symptoms experienced by the runners during the week prior to the race were grouped into clusters of symptoms, 530 runners (7.5%) experienced acute systemic symptoms, 896 runners (12.7%) experienced acute respiratory symptoms and 249 runners (3.5%) experienced acute gastrointestinal symptoms. In addition, 6157 runners (87.5%) passed the “neck check”, while 878 runners (12.5%) failed the check.

3.4.2. The did-not-start (DNS) rate (% runners) in different groups

In the cohort of 7035 runners, 6535 runners (92.9%) started the race and 500 runners (7.1%) did not start the race. Of the 500 runners who did not start, 355 runners did not experience any symptoms of an acute illness in the 7 days prior

to the race, while 145 runners did experience symptoms of an acute illness during the 7-day period prior to the race.

The did-not-start (DNS) rate (% runners) in different groups and sub-groups is depicted in Table 3.2. The DNS rate for the control group (asymptomatic runners) was significantly lower (6.2%) and the DNS rate for the symptomatic group (10.8%) ($p<0.0001$).

In the sub-groups of symptomatic runners, the DNS rate for the runners with systemic symptoms was highest (14.7%), and this was significantly higher than the control group ($p<0.0001$). Runners who experienced gastrointestinal symptoms also had a high DNS rate of 12.1% ($p=0.0003$ vs. the control group), while runners who experienced respiratory symptoms had a DNS rate of 11.7% ($p<0.0001$ vs. the control group). Similarly, the DNS rate for the runners who failed the “neck check” was 12.2% ($p<0.0001$ vs. the control group).

Table 3.2. The did-not-start (DNS) rate (% runners) in different groups and sub-groups

Group	Sub-group	Percentage of runners	P-value *
Control group		6.2%	
Symptomatic group		10.8%	<0.0001
	Systemic symptoms	14.7%	<0.0001
	Respiratory symptoms	11.7%	<0.0001
	Gastrointestinal symptoms	12.1%	0.0003
	Failed “neck check”	12.2%	<0.0001

*: p value vs. control group

3.4.3. The did-not-finish (DNF) rate (% of runners who started the race) in different groups

Six thousand five hundred and thirty-five (6535) runners of the 7035 runners in this cohort started the race. Of these runners who started, 6413 runners (98.1%) finished the race and 122 runners (1.9%) did not finish. Of the 122 runners who did not finish, 96 runners did not report any symptoms during the 7 days prior to the race, while 26 runners did report symptoms of an acute illness in the 7 days prior to the race.

The did-not-finish (DNF) rate (% runners) in different groups and sub-groups is depicted in Table 3.3. The DNF rate for the control group (asymptomatic runners) (1.8%) was similar to that of the symptomatic group (2.2%) (p=0.3778).

Runners who experienced systemic symptoms in the 7 days prior to the race had the highest DNF rate (2.7%) (p=0.1954 vs. control), followed by the runners who experienced gastrointestinal symptoms during the 7 days prior to the race (2.3%) (p=0.16 vs. control) and runners who experienced respiratory symptoms (1.8%) (p=0.9571 vs. control). Runners in the failed “neck check” group had a DNF rate of 2.2% (p=0.4319 vs. control).

Table 3.3. The did-not-finish (DNF) rate (% runners who started the race) in different groups and sub-groups

Group	Sub-group	Percentage of runners	P-value *
Control group		1.8%	
Symptomatic group		2.2%	0.3778
	Systemic symptoms	2.7%	0.1954
	Respiratory symptoms	1.8%	0.9571
	Gastrointestinal symptoms	2.3%	0.16
	Failed “neck check”	2.2%	0.4319

*: p value vs. control group

3.4.4. The medical complication (MC) rate (% runners who started the race) in different groups

Of the 6535 runners who started the race, 16 runners were admitted to the medical facilities during the race, while 6519 runners did not need medical attention. Of the 16 runners who required medical attention, 12 runners did not report any pre-race symptoms of an acute illness, while 4 runners reported symptoms of an acute illness in the 7-day period prior to the race.

The medical complication (MC) rate (% runners) in different groups and sub-groups is depicted in Table 3.4. The MC rate of the control group was 0.22% and that of the symptomatic group was 0.34%, but this was not significantly different between the two groups (p=0.4844). The MC rate of the runners who passed the “neck check” was 0.24% and the rate for the runners who failed the “neck check” was 0.26% (p=0.9306). The runners who experienced systemic symptoms during the 7 days prior to the race had a MC rate of 0.44% (p=0.3782).

Table 3.4. The medical complication (MC) rate (% runners who started the race) in different groups and sub-groups

Group	Sub-group	Percentage of runners	P-value *
Control group		0.22%	
Symptomatic group		0.34%	0.4844
	Systemic symptoms	0.44%	0.3782
	Passed “neck check”	0.24%	0.9306
	Failed “neck check”	0.26%	0.9306

*: p value vs. control group

3.4.5. Summary of the main outcome variables

A summary of the main outcome variables in the symptomatic and control group is depicted in Table 3.5. The DNS rate was significantly higher in the symptomatic group compared with the control groups, while the DNF and MC rates were similar between the two groups.

Table 3.5. The DNS rate, DNF rate and MC rate for the control and symptomatic groups

	Control group	Symptomatic group	P-value
DNS rate	6.23%	10.84%	<0.0001
DNF rate	1.8%	2.18%	0.3778
MC rate	0.22%	0.34%	0.4844

3.5. Discussion

The main findings of this study were as follows: 1) 19.2% of runners in this cohort reported symptoms of an acute illness in the 7-day period prior to an endurance race, 2) the most common symptoms of acute illness were sore throat (34.5%), runny nose (29.9%), general tiredness (27.8%), blocked nose (23.3%) and headaches (22.6%), 3) 12.7% of runners reported acute respiratory symptoms, 7.5% of runners reported acute systemic symptoms, and 3.5% reported acute gastrointestinal symptoms, 4) 12.5% of runners reported symptoms that would result in a failed “neck check”, 5) runners who reported symptoms of acute illness, and who were given educational information, had a significantly higher did-not-start (DNS) rate compared with control (no reported symptoms) runners, 6) runners who reported symptoms of acute illness, and who were given educational information but decided to start the race, had a similar did-not-finish (DNF) rate compared to control runners, and 7) runners who reported symptoms of acute illness, and who were given educational information, but then decided to start the race had a similar medical complication (MC) rate compared to control runners.

3.5.1. Period prevalence of runners with symptoms of an acute illness 7 days prior to the race

In this study, 19.2% (N=1338) of runners reported one or more symptoms of an acute illness in the 7 day period prior to the race. This percentage is lower than the 40% of athletes who reported an episode of an URT illness in the 8 week period prior to the 1987 Los Angeles Marathon (14), but is similar to the 17% of runners who reported symptoms of an infectious episode in the 3 week period prior to the 2000 Stockholm Marathon (18). However, a strict comparison with the prevalences is not valid because different definitions of illness were used, and the period (1 week, 3 weeks and 8 weeks) differs between studies. However,

these data do indicate that a significant percentage of runners experience symptoms of acute illness in the 1-8 weeks prior to a race.

In our study, the most common symptom indicated by the symptomatic group (N=1338) was a sore throat followed by a runny nose, general tiredness and a blocked nose. Symptoms of an acute respiratory illness were therefore most common. These data are consistent with many studies showing that acute respiratory illness is the most common acute illness in athletes before and during competition ((1), (5), (6), (7)). Therefore the most common illnesses amongst runners are acute respiratory conditions (URT illness), followed by gastrointestinal disorders and then dermatological conditions.

However, in our study we note that 8% of runners reported a fever, 12.7% symptoms of an acute systemic illness, and 12.5% reported symptoms that would constitute a failed “neck check”. These data are of concern as systemic illness can affect a number of organ systems including skeletal muscle (myositis) and the cardiac muscle (myopericarditis) ((1), (3), (8)). These runners may therefore be at a particular risk of developing medical complications (including life-threatening complications) during a race. It is for this reason that we included an educational intervention program, as part of this study, to inform runners of the potential medical complications that may result from exercising while suffering from an acute systemic illness.

3.5.2. Did-not-start (DNS) rate

It is well established, from data obtained through the race organisers, that a percentage of runners who enter for a race, complete the registration process in the days prior to the race, still elect not to start the race on race day. We recognize that there are many possible reasons for this. However, in this study, we provided all the runners in our cohort of 7035, who reported symptoms of an acute illness in the 7 days before the race, with targeted educational information

and guidelines for safe participation when they suffer from acute illness. In our study the DNS rate was significantly higher in the symptomatic group (10.8%) compared to the control group (6.2%). On the assumption that all the other possible factors that could influence runners in a decision to not start the race were similar between the two groups, we conclude that the higher DNS rate in the symptomatic group was as a result of the educational information that was provided. We cautiously conclude that the educational information was effective in increasing the DNS rate in runners with more severe illness that could lead to a potential medical complication. In particular, we note that in sub-groups with a potential higher risk for medical complications the DNS rate was higher: systemic symptom group (14.7%), failed “neck check” group (12.2%), and gastrointestinal symptom group (12.1%). It is well established that clinical guidelines consistently report that systemic symptoms is a contraindication to participate in sport ((2), (3), (8), (12), (15), (30)).

These data indicate that an acute pre-race illness screening process can identify runners with acute illness symptoms, that educational intervention can be applied, and this is related to an increased rate of deciding not to start a race. However, we did not have a group of runners in our study with reported symptoms but who did not receive educational information as a comparison. The inclusion of such a group in our study was not possible for ethical reasons. Therefore, we cannot attribute the increased DNS rate solely to the screening and educational intervention program. It is for this reason that we wanted to track runners that made the decision to start the race and determine whether the did-not-finish and the medical complication rates were different in the symptomatic and control groups.

3.5.3. Did-not-finish (DNF) rate and the medical complication (MC) rate

The main finding in the DNF rate was that this was similar in the control group (1.8%), the symptomatic group (2.18%) and the sub-groups within the

symptomatic group: systemic symptom group (2.7%), respiratory symptom group (1.8%), gastrointestinal symptom group (2.3%), and the failed “neck check” group (2.2%). Similarly, the MC rates in the control group (0.22%) was similar to that in the symptomatic group (0.34%).

These data indicate that runners who reported pre-race symptoms of acute illness, and who then received educational information, and then decided to start the race, did not have a higher rate of not finishing the race or developing medical complications. We acknowledge that factors other than the information in the educational intervention could contribute to the decision to not start the race. However, as mentioned it appears that the screening and educational information did increase the DNS rate, and that those runners who did start the race despite pre-race illness did not have an increased rate of not finishing or developing medical complications.

However, we do note that the MC rate in the sub-group of runners with systemic symptoms, was 0.44% and that this rate was higher than the control group and the symptomatic group. This was not statistically significant, and we note that this is perhaps as a result of a small sample size. This requires further investigation and a larger prospective cohort study.

In summary, when the results of the DNS rate, DNF rate and MC rate are taken into consideration, it appears that the screening and educational intervention prior to the race (information leaflets) resulted in an increase in the DNS rate, and that this “filtered” higher risk runners from those at lower risk of not finishing or developing medical complications during the race (similar DNF and MC rates). These data are novel, and we do not have similar studies for comparison.

3.5.4. Strengths and limitations of the study

The main strengths of our study are that it is novel, that we screened a large number of runners, and that we were able to track the cohort accurately and successfully during the race period. However, our study also had some limitations. We were not able to obtain data from all runners who entered the race and had a modest response rate of 27.6%. However, this limitation would only affect the accuracy of the prevalence data, and would not affect the impact of the screening and educational intervention as the compliance to follow-up of the final cohort was 100%. We also acknowledge that there was no clinical diagnosis made on the ill runners and the data captured relied on self-reported symptoms by the runners. It is thus possible that some symptoms reporting was inaccurate, for example, a sore throat and runny nose could have been due to allergies as opposed to an infection, and generalised body pains and tiredness could have been due to a chronic condition and not due to an acute illness. We also acknowledge that in our control group some runners might not have reported symptoms. Finally, as previously mentioned, we do not know all the possible reasons for runners not starting or not finishing the race. We can therefore not assume that the DNS, DNF and MC rates were only as a result of an acute illness, or subsequent advice given to them through the educational intervention. In future studies, data to determine the precise reasons for not starting or not finishing should be obtained from runners.

3.6. Summary and conclusion

It has been well established that the most common acute illnesses affecting athletes are URT illnesses, with the prevalence varying in studies from 17% to 40%. In our cohort of 7035 runners, 1138 runners (19.02%) experienced symptoms of an acute illness in the 7-day period prior to the race. The most common symptoms experienced were that of an acute respiratory illness (12.7%), followed by symptoms of a gastrointestinal illness (3.5%). Five hundred

and thirty (530) runners (7.5%) experienced symptoms of an acute systemic illness, while 878 runners (12.5%) failed the check.

The did-not-start rate for the symptomatic group was 10.8%, which was significantly higher than the DNS rate of the control group (6.2%). The DNS rate for the runners with systemic symptoms was highest at 14.7%, whilst the DNS rate for the runners who failed the “neck check” was 12.2%. Both these groups DNS rates were also significantly higher than the control group. It is thus clear that those runners who reported symptoms of acute illness, and who were given educational information, had a significantly higher DNS rate compared with the control runners. We thus conclude that the higher DNS rate in the symptomatic group was as a result of the educational information that was provided and we cautiously conclude that the educational information was effective in increasing the DNS rate in runners with more severe illness that could lead to a potential medical complication.

The DNF rate for the symptomatic group was 2.2%, which was similar to that of the control group, which was 1.8%. Runners who experienced systemic symptoms in the 7 days prior to the race had the highest DNF rate (2.7%), whilst runners who failed the “neck check” had a DNF rate of 2.2%. Similarly, the medical complication rate did not differ much between the control group (0.22%), the symptomatic group (0.34%), the systemic symptom group (0.44%) and the group who failed the “neck check” (0.26%). From these data, it is clear that runners who reported symptoms of acute illness, and who were given educational information but decided to start the race, had a similar DNF rate and MC rate compared to control runners. From this we conclude that runners who reported pre-race symptoms of acute illness and who received educational information, and then decided to start the race, did not have a higher risk of not finishing the race or developing medical complications. Runners who decided to run despite their symptoms of acute illness, made the correct decision with the help of the guidelines provided.

Our study thus indicates that a screening process can identify runners with acute illness symptoms, and that educational intervention can be applied and this is related to an increased rate of not starting a race, no increase rate of not finishing the race, and no increased medical complication rate. From a practical clinical point of view, the screening and educational interventional program made it safer for the runners to participate in the endurance race. Perhaps further studies should be done on even larger cohorts to validate our findings, after which such a program can be implemented in other endurance sports events as well.

Chapter 4

Summary and conclusion

4.1. Summary of main findings

The focus of this dissertation was acute illness in athletes, particularly focusing on acute illness in endurance runners in the 7-day pre-race period, how illness affects the decision to participate, and the ability to finish a race without medical complications. The feasibility and what impact a screening process and educational intervention guideline program would have on making the race safer for athletes with an acute illness was studied.

In Chapter 2, the period prevalence of runners with an acute illness one week prior to an endurance race was firstly reviewed. There were only 2 studies conducted to ascertain such a period prevalence, but the periods were 2 months prior to a race and 3 weeks prior to a race respectively. From an epidemiological perspective, the review indicated that an URT infection was the most common illness amongst athletes, followed by gastrointestinal disorders and dermatological conditions. However, the researchers utilized self-reported questionnaires in these studies, and a clinician never made a diagnosis of an URT infection. As such, other causes for URT illness symptoms in athletes needs to be considered, such as allergic rhinitis. It is however well documented that exercising with an acute illness is not without risk and potential medical complications include myocarditis, rhabdomyolysis with acute kidney failure and sudden cardiac death. Infections, including URT infections, also have an influence on several systems in the body, including the cardiovascular, neurological and muscular systems, thermoregulation and metabolic processes.

These effects all culminate into a negative effect on the athlete's exercise performance.

The review further indicated that there are very little data available to validate the "neck check" (safe to exercise with local URT symptoms and unsafe to exercise with systemic symptoms or lower respiratory tract symptoms) as a clinical guideline to advise an acutely ill athlete on participation in an exercise session or race. The value of ascertaining the influence of an intervention educational program (guidelines based on the "neck check" and various available return-to-play guidelines) on the safe participation of acutely ill runners was again confirmed. Finally, the review also showed that there is no evidence in the literature pertaining the DNS rate or the DNF and MC rates of runners after an acute illness screening process has been completed. With these questions in mind, the original research component was undertaken.

The research study in this dissertation was conducted on a cohort of 7035 runners. In this cohort, the period prevalence of runners with an acute illness in the 7-day period prior to the race was 19.02%, and the most common symptom experienced by the runners was a sore throat, followed by a runny nose. These findings support the evidence in the literature that an URT illness is the most common illness amongst endurance athletes. In the control group (asymptomatic runners) 6.2% of the registered runners did not start the race (DNS rate), and this was significantly lower than the DNS rate for the runners with acute illness symptoms who then received educational material as an intervention (10.8%). The DNS rate for the runners with systemic symptoms was highest (14.7%) and this was significantly higher than the control group, as was the DNS rate for the runners who failed the "neck check" (12.2%). We suggest that the higher DNS rate in the symptomatic group was (in part) as a result of the educational information that was provided. We cautiously conclude that the educational information was effective in reducing the number of runners with an acute illness to start the race. Furthermore, runners with more severe illness (systemic

symptoms) also withdrew from running on race day, thereby reducing the risk of a potential medical complication.

The DNF rate for the symptomatic group was 2.2%, which was similar to that of the control group (1.8%). Runners who experienced systemic symptoms in the 7 days prior to the race had the highest DNF rate (2.7%) and runners in the failed “neck check” group had a DNF rate of 2.2%. Similarly, the MC rate of the control group was 2.2%, which was similar to the MC rate of the symptomatic group (0.34%), the failed “neck check” group (0.26%) and the group who had systemic symptoms (0.44%). These data indicate that runners who reported pre-race symptoms of acute illness and who received educational information, and then decided to start the race, did not have a higher risk of not finishing the race or developing medical complications. These data provide the first evidence that a screening and educational information program for acute illness can increase the DNS rate, and therefore those runners who did start the race despite pre-race illness, did not have an increased risk. These data are novel, and we do not have similar studies for comparison.

4.2. Clinical implications of findings

As we cautiously conclude from our study that the screening and educational intervention program led to a higher DNS rate in the symptomatic group and in runners with more severe illness that could lead to a potential medical complication, and as the data indicated that those runners who did start the race despite pre-race illness did not have an increased risk, we make the following suggestions:

1. In future, all athletes could be screened for an acute illness prior to an endurance race and given appropriate educational material.
2. Social media could play an important role in this process.

3. Athletes with symptoms of an acute illness should receive education, in the form of a leaflet, pertaining their illness. This information leaflet should have the contraindications for exercising on them.
4. A medical facility could be made available at the registration venue where athletes can go for a medical check-up if they are uncertain whether to participate in the race. This process should include a physical examination, as some symptoms of an URT illness are due to causes other than infection.
5. Athletes should be educated on possible medical complications when they exercise, in particular when exercise is contraindicated so that they understand the risks involved and can make an informed decision on participation.

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 areas for research should be considered in a larger cohort:

1. Other possible reasons (i.e. not due to the educational intervention program or due to illness) for the did-not-start rate.
2. Other reasons (i.e. not due to illness) for the did-not-finish rate.
3. Possible medical complications that only developed later (i.e. a couple of hours or of day after the race), such as rhabdomyolysis.
4. Our screening process relied on self-reported symptoms and it is thus possible that some diagnosis of an “acute illness” could indeed have been a non-infective condition, such as an allergy. Future studies should include a physical examination, and possibly special investigations, to make a more accurate diagnosis.

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Appendices

Appendix A

Pre-race questionnaire

Email to runners

Subject of email: Your Old Mutual Two Oceans Marathon: Important information

Dear [insert name]

Congratulations for coming this far! It is only a few days to go before your race. We trust that your training and preparation has been going well.

Here is your final medical check list before race day:

Final medical checklist for [Insert name]

1. Completed medical questionnaire on entry– Yes

2. Received medical information in newsletters – Yes

3. Medical information in the race magazine – Please read

4. Medical aid and next of kin details on your race number – Please complete after registration

5. Last minute information about running and flu/infections – Please click here to answer a single question

We wish you all the best for the race.

The Two Oceans Medical team

Running and symptoms of an acute infection

Symptoms of acute illness and infections such as flu, gastro-enteritis (upset stomach) and other infections (e.g. bladder) are more common in runners just before a race (after periods of peak training). Running with symptoms of an infection can increase the risk of medical complications during the race.

The symptoms of infections vary but include the following: generally not feeling well, fever, general muscle pain, general joint pain, general tiredness, headache, sore throat, blocked or runny nose, sore ears, cough, wheeze, diarrhoea, nausea, vomiting, or abdominal cramps/pain.

Please answer the following question so that we can give you advice:

Do you have any of these symptoms of acute illness (today or in the last 7 days)

No ☐

Yes ☐

Question 2: Symptoms of an acute infection or illness	
Symptoms of an acute infection or illness You indicated that you have symptoms of an acute illness **(today or in the last 7 days)** **Please indicate which symptoms do you have?** (Please tick on all the symptoms you have i.e. you may chose more than one) (Based on your responses, you will be sent some information to assist you)	☐ Fever ☐ Sore throat ☐ Runny nose ☐ Blocked nose ☐ Sore ears ☐ Wheezing ☐ Cough ☐ General muscle pains ☐ General joint pains ☐ Headache ☐ General tiredness ☐ Nausea ☐ Vomiting ☐ Diarrhoea ☐ Abdominal pain or cramps ☐ Skin rash / infection ☐ Symptoms of a bladder infection ☐ Any other symptoms (Please specify:)_____

Appendix B

Information leaflets

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. Usually, but not always, these infections result in no 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.
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. 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.

Two Oceans Medical Team

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

Guidelines

Running and acute infections

Runners that are training very hard may be more susceptible to acute 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.

Two Oceans Medical Team

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

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. 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.

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.

Two Oceans Medical Team

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

Appendix C

Approval of Research Ethics Committee of the Faculty of Health Science at the University of Cape Town

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 July 2014

HREC REF: 009/2011

Prof M Schwellnus
Sports Science Institute

Dear Prof Schwellnus

PROJECT TITLE: TWO OCEANS ULTRA-MARATHON 2011: MEDICAL CONSEQUENCES FOLLOWING ENDURANCE SPORTS (With extension to the 2013 race)

The HREC confirms that the MPhil Sport & Exercise Medicine student, Dr Anri van Tonder, 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