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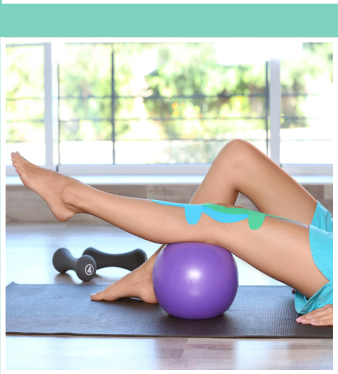

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REVIEW

ANTI-DOPING

Anti-doping and other sport integrity challenges during the COVID-19 pandemic

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ABSTRACT

The coronavirus disease (COVID-19) pandemic has had an unprecedent impact on the world of sport and society at large. Many of the challenges with respect to integrity previously facing competitive sport have been accentuated further during the pandemic. Threats to the integrity of sporting competition include traditional doping, issues of technological fairness, and integration of transgender and intersex athletes in elite sport. The enforced lull in competitive sport provides an unprecedented opportunity for stakeholders in sport to focus on unresolved integrity issues and develop and implement long-lasting solutions. There needs to be a concerted effort to focus on the many technological innovations accelerated by and perfected during COVID-19 that have enabled us to work from home, such as teaching students on-line, applications for medical advice, prescriptions and referrals, and treating patients in hospitals/care homes via video links and use these developments and innovations to enhance sport integrity and anti-doping procedures. Positive sports integrity actions will require a considered application of all such technology, as well as the inclusion of "omics" technology, big data, bioinformatics and machine learning/artificial intelligence approaches to modernize sport. Applications include protecting the health of athletes, considered non-discriminative integration of athletes into elite sport, intelligent remote testing to improve the frequency of anti-doping tests, detection windows, and the potential combination with omics technology to improve the tests' sensitivity and specificity in order to protect clean athletes and deter doping practices.

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KEY WORDS: Pandemics; Sports; Doping in sports; Technology; Transgender persons.

The COVID-19 pandemic, officially declared in March 2020,[1] has had major economic, social and political impact,[2] forcing governments to take action to contain the spread of the virus such as quarantine, lockdown, case-finding, contact tracing and mask-wearing.[2] In the context of sports and physical activity, the collateral effects of the actions against the pandemic resulted in a reduction of the levels of physical activity in the general population[3] and changes in the daily routine and competition plans of athletes.[4] Since the beginning of the world-wide virus outbreak, social distancing strategies have been adopted by governments and sporting events have not been exempt.[5] Many sporting events have been postponed or cancelled since the beginning of the pandemic including the postponement of the Tokyo 2020 Olympic Games,[4] as many athletes (and general population) lost access to their training facilities.[6] The impact of these measures has been varied, with athletes reporting increased stress and dysfunctional

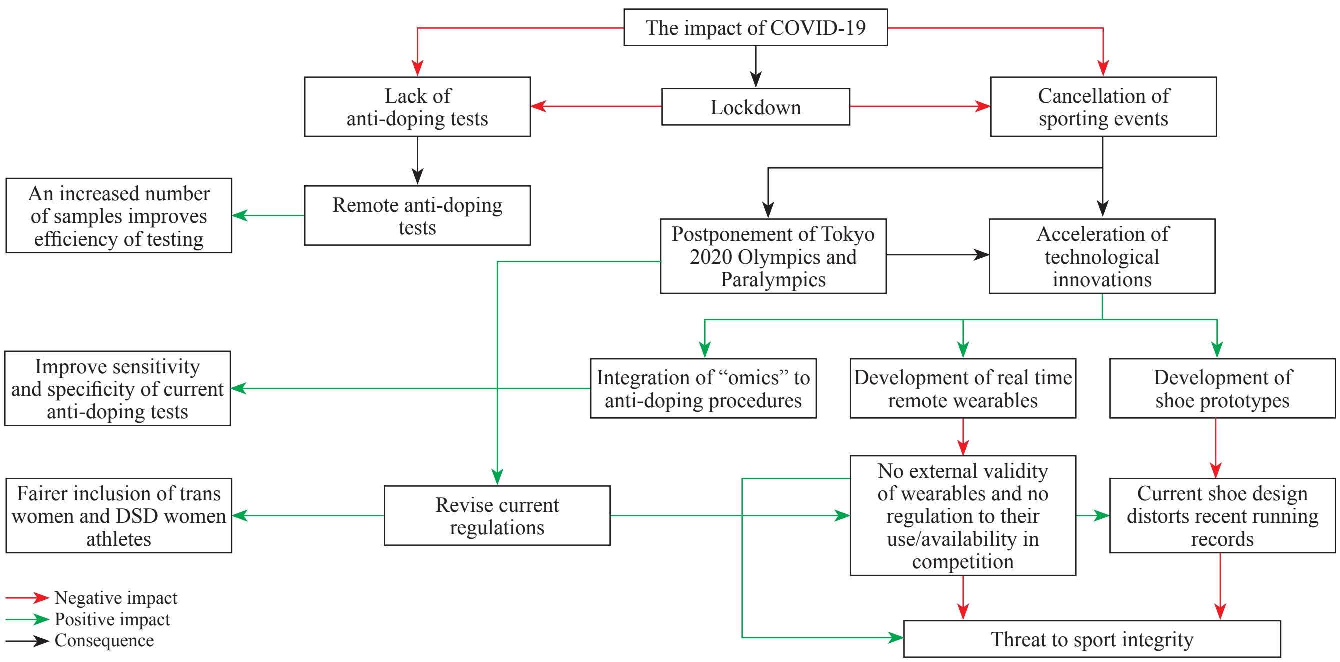

Figure 1.—Diagram summarizing the consequences and impact of COVID-19 on sports integrity.

psychobiosocial states,[4] as well as slower levels of tolerance and higher levels of alexithymia, anxiety, stress, and depression.[7] In non-athlete populations such as in the Italian region of Lombardy (the region with the highest prevalence rate of COVID-19 compared to the rest of Italy), significantly higher level of anxiety, lower levels of motivation to participate in physical activity, and less time spent in physical activity were reported during the quarantine.[8] Athlete populations have also been affected by quarantine measures, for instance, the majority of South African elite and semi-elite athletes that took part in a survey on training habits during COVID-19 have reported training alone, limited sport-specific training and a reduced training load.[9] In addition, more than half of the athletes felt depressed and admitted to the worsening of their diet. Notably, these "side-effects" of training during COVID-19 were reported at a higher rate in female athletes compared to males.[9] The challenges faced by athletes due to COVID-19 lockdown restrictions has limited some important aspects of training such as quality, volume, intensity and specificity, leading in most cases to detraining and deconditioning.[10] Detraining is expected to result in many training adaptations being reversed such as muscle capillary density, myoglobin concentration, fiber cross-sectional area (CSA) and strength.[11] For example, only 15 days without training led to a 6.3% and 4% reduction of muscle capillary density and maximal oxygen uptake ($\dot{V}O_2max$) respectively in well-trained endurance runners[12] and 14 days detraining in power athletes reduces fiber CSA by 6.4%[13] and results in a 5.8% lower strength in endurance-trained male athletes.[14] Not only does detraining reduce key performance indices, but the resumption of high-level training after a period of detraining also increases injury risk.[15] Therefore, it is important for athletes to maintain even a modest amount of training, to prevent the associated fitness decline and reduce injury risk on training resumption.[16] Some coping strategies have been adopted during the confinement period, with the majority utilizing a virtual environment and online training tools. For example, 329 cyclists using online training tools throughout lockdown restrictions in Spain reported a higher frequency and duration of training compared to those cyclists who did not use online tools.[15] These alternative solutions to maintain training load and the reduced/lack of competitions have benefited some athletes as returning to competition has seen a number of world and national records, as well as personal bests, which may also have been aided by recent innovations in shoe technology (issue described below).

While sporting events around the world were being postponed/cancelled, anti-doping efforts were also being affected with "an absence or diminished level of testing on athletes in areas of higher risk".[17] In the context of the con-

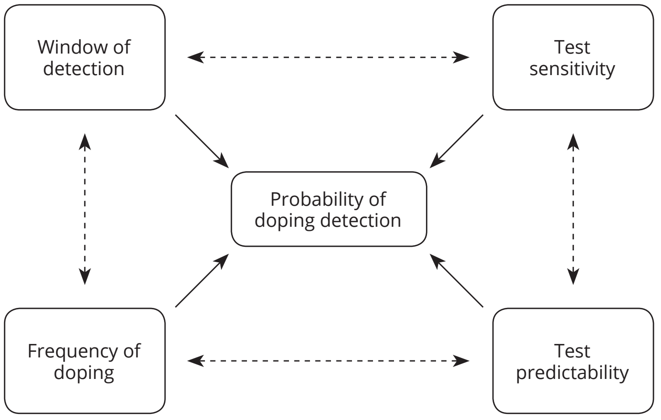

Figure 2.—Graphic representation of the factors influencing the probability of detection and their interrelationships.[23]

siderable restrictions in place across the globe, collecting and analyzing anti-doping samples has been problematic leading to a potential increase in the use of performance enhancing drugs (PEDs). China Anti-doping Agency was the first major anti-doping authority to suspend anti-doping in February 2020.[18] This measure to suspend anti-doping quickly spread across the globe along with the virus. Out-of-competition testing is one of the most important strategies utilized by anti-doping authorities to prevent doping especially in the build-up to major sporting events like the Olympics because of the unpredictable nature of visits by anti-doping control officers. A diagram outlining the consequences and impact of COVID-19 on sports integrity, that sets the scene for the present article, is displayed in Figure 1. While the priority should be the health and safety of athletes and doping control personnel, anti-doping authorities and stakeholders are in a difficult situation as a result, with reduced, or at worse, lack of testing over the past 12 months.

Anti-doping challenges

The World Anti-doping Agency (WADA) was established in 1999 and the WADA Code was implemented in 2004 in order to regulate doping control and provide educational strategies to avoid doping.[19] However, more than 20 years since the foundation of WADA and a decade after the implementation of the Code in its numerous editions, the prevalence of doping in sport has not substantially abated.[20] The true prevalence of doping in sport is unknown but substantially higher than the cases detected.[20, 21] The strategies for doping control cited in the Code are: Education, Deterrence, Detection, Enforcement and Rule of law.[22] An important prerequisite for a successful anti-doping program is an effective testing system able to detect doping, however the current anti-doping system, despite some positive aspects, remains broadly inefficient and ineffective.[23] Hermann and Henneberg[23] suggested that current anti-doping systems in sport are "*doomed to fail*" due to four elements (*i.e.*, window of detection, doping regime, test predictability, and test sensitivity) that impact the probability of doping detection (Figure 2).[23] They estimate the likelihood of doping detection using the product of the window of detection in hours as a fraction of a week (*i.e.*, hours of window of detection/168 hours), the test sensitivity (in percentage), how often doping occurs (*i.e.*, 1.0=continuous use and 0.5=intermittent use), and the test predictability, expressed as the number of tests that doped athletes expect to occur per year, divided by the number of weeks in the year. Herman and Henneberg give the example that, with a 24 hours window detection, a 40% test sensitivity, continuous use and one test a month, the estimated probability of a successful test is 0.014%, while even a window detection of 5 days, the probability of success of detection in a single test is 0.0714%. In order to improve the current doping system, authorities need to increase test sensitivity, the window of detection, and the number of collections throughout the year.[23]

The long-term effects of certain PEDs also affect the efficacy of anti-doping testing. For example, the consensus in the very limited scientific literature is that supra-physiologic levels of exogenous anabolic androgenic steroids (AAS) such as testosterone, stimulates muscle growth and consequently an increase in muscle mass and strength.[24] The suggested mechanism for the increase in muscle hypertrophy and potentially the performance-enhancing properties induced by testosterone is an increase in the number of satellite cells and myonuclei.[25] There are large numbers of myonuclei in skeletal muscle fibers and according to the notion of the "myonuclei domain", each controls a limited cytoplasmic area.[26] Most available evidence would indicate that muscle fiber hypertrophy, induced by resistance-type exercise training, is accompanied by a rise in myonuclear and satellite cell content.[27] The premise of the long-term performance-benefits of AAS is encapsulated in the term "muscle memory" which describes the phenomenon where myonuclei acquired by exercise and/or testosterone administration during hypertrophy are not lost after a period of detraining and atrophy.[28] A "muscle memory" mechanism could explain the observation that strength training adaptations induced by an increase in muscle mass are significantly enhanced in previously trained individuals despite a prolonged detraining period.[29] In particular, the formation of extra myonuclei could be the local "memory" mechanism in muscle.[28, 29] The significance of this hypothesis is that either a long- or short-term exposure to AAS will have a sustained effect on muscle morphological changes, leading to improved performance and an enhanced future training effect. Given the persistence of muscle nuclei, the use of AAS combined with training will have a greater impact on muscle hypertrophy than either training or steroid use alone. Previous studies using animal models support this idea. For example, in a mouse model, female mice were subjected to testosterone propionate for 14 days, resulting in a 66% increase in myonuclei number and a 77% increase in fiber CSA in the Soleus muscle.[29] The number of muscle nuclei remained elevated (28% higher compared to control) 3 months (approximately 12% of lifespan) after withdrawal of the drug with no difference in fiber CSA and fiber type. Following testosterone withdrawal, a 6 days overload intervention in these animals resulted in a 31% increase in the fiber CSA (*vs.* 6% in control) and this increase in CSA remained 20% higher relative to controls following 14 days of overload. The overload exercise was applied by synergist muscle ablation in either the oxidative/slow Soleus or the glycolytic/fast extensor digitorum longus (EDL) muscle. However, the effect reported in the EDL was less dramatic than in the Soleus. One likely explanation for this observation is the fact that the Soleus is an oxidative postural muscle and therefore less functionally relevant for strength performance. If the outcome of this research is directly transferable to humans, the 3-month detraining period of the mice in the animal study, would correspond to a decade for humans and therefore have major implications for the long-term use of AAS for clinical treatment, doping in sport and integration of transgender and differences of sex development (DSD) athletes in elite sport.

Given the above, one key challenge due to the pause or reduction in anti-doping testing during COVID-19 is the potential for athletes to have abused substances that might have long-term benefits on performance beyond the life of the PED since the "muscle memory" acquired by both exercise and/or testosterone administration during hypertrophy are not lost after a period of detraining and atrophy[28] as discussed above. The long-term effect of muscle memory has implications for anti-doping policies and penalties. At least 120 athletes with a history of doping offenses and who had been suspended for a doping violation competed at the 2016 Rio Olympics. Thirty-one of these athletes (approximately 25%) won medals.[30] Eight of these were weightlifters who were suspended from March 2013 up to October 2015 for Anti-doping Rule Violations (ADRVs).[31] Considering the long-term effect of muscle memory, it is possible that athletes were still benefiting from the effects of AAS during the 2016 Games. The performance enhancing benefits of AAS are well established, however there are several limitations in detecting the use of AAS such as: 1) noticeable variation of endogenous production and metabolism of human sexual steroid hormones; 2) rapid advances in AAS designs, which complicate the detection of these novel AAS; 3) use of diuretics or probenecid to decrease urinary concentration; and 4) intermittent use of AAS with very short half-lives.[32] As directly implied by the equation previously described by Hermann and Henneberg,[23] the detection of AAS is challenging even during normal circumstances without a pandemic and associated restrictions. During the COVID-19 lockdown restrictions, WADA and stakeholders suspended or reduced doping control programs (including testing and other activities)[33] and in doing so inadvertently provided athletes wishing to misuse AAS an extraordinary opportunity to do so without any chance of being caught.

The last major anti-doping development aimed at providing a step change in anti-doping testing was the Athletic Biological Passport (ABP) implemented in 2009 as a strategy for blood doping detection (or Hematological Model) and the urinary Steroidal Model implemented in 2011.[32] The ABP uses Bayesian inference techniques and longitudinal measurements of blood parameters providing a significant advance in doping detection.[34] However, the ABP Hematological Model presents some limitations due to confounding factors such as the natural physiological response to altitude training. Altitude training can lead to hematological adaptations that may be relevant to the ABP, while the administration of micro-doses of rHuEPO may not cause hematological fluctuation large enough to be detected.[35] In terms of the ABP steroidal model, the testosterone to epitestosterone concentration ratio can being affected by many factors such as genetics and inter-individual variation, gender, age and circadian rhythms.[36] For example, a genetic polymorphism in the gene coding for the enzyme uridine diphosphate glucuronosyltransferase 2B17 leads to significantly lower urinary testosterone to epitestosterone glucuronide ratio.[37]

The next frontier in anti-doping testing

Considering the equation proposed by Hermann and Henneberg,[23] test sensitivity and the detection window of substances are crucial for the success of any anti-doping system. The investment and development of new methods/technologies that can be used in combination with, or independently of, current methods, are important to keep anti-doping system ahead of individuals who would seek to avoid detection. New advances in biotechnologies and "omics"-based methods enable the use of molecular biology as powerful tools which have been successfully applied to diverse fields such as diagnosis of cancer[38] and rare diseases with vast clinical and genetic heterogeneity.[39] "Omics" technologies can be used to enhance current anti-doping testing, as shown in previous studies that investigated the blood transcriptional signature after administration of recombinant human erythropoietin (rHuEPO) in endurance trained athletes.[40, 41] Transcriptional profiling showed that transcripts were altered by rHuEPO administration and the expression pattern was observed up to 3 weeks after the last rHuEPO injection.[40] A validation study using micro-dose rHuEPO provided evidence that transcriptional biomarkers may be used to prolong the detection window of blood doping.[41] This study revealed that 15 out of the 41 analyzed transcripts showed a high sensitivity (≥ 93%) with specificity equal to or above 71%.[41] When applying these outcomes in the formula proposed by Hermann and Henneberg,[23] using the same scenario cited above, we have the window of detection equal to or more than one week (*i.e.* W=1), sensitivity (S) of 0.93, with a person continuously doping (D=1.0) and test predictability (T) of 0.25, the probability of success increases from 0.014 to 0.23 – while still not satisfactory, but when combined with longitudinal measures used by the ABP, the efficacy of the testing system increases.

Despite the need for more testing, there are important limitations associated with multiple testing such as the costs of sample analysis, the need for laboratory personnel, shipping costs and need for storage. WADA favurs the use of dried blood spot (DBS) as a simpler, faster and cheaper method of collection. DBS was used as a sampling method when Robert Guthrie introduced the concept of "neonatal screening" where capillary blood, obtained from pricking the heel or finger and blotted onto filter paper, could be used to detect numerous diseases in large populations of neonates.[42] The advantages of DBS include 1) the use of a small blood volume; 2) a less invasive collection; 3) no phlebotomist is required (in most countries); 4) lower transport costs due to the small volume; 5) samples can be stored at room temperature; 6) less space for long-term storage is required; and 7) the volumes are enough for forensic DNA identity testing which could be used to confirm the identity of the provider of the sample. Despite these many advantages, there are concerns regarding the real applicability of DBS, such as the limited number of analyses that can be carried out due to the small volume of sample collected (*i.e.*, typically less than 100 µL of blood). However, previous studies have shown that DBS can be combined with gene expression analysis,[43-45] which offers a larger window of detection (with particular focus on rHuEPO) with at least 24 genes differently expressed even 3 weeks after the last dose of rHuEPO administration.[41] Three of these genes (*ALAS2*, *CA1*, and *SLC4A1*) were also investigated in other studies that used RNA-based detection methods and these were successfully adapted for extraction and detection of rHuEPO from DBS samples,[44, 45] while also showing comparable outcomes using both an automated and manual method of RNA extraction.[45] The combination of both methods (*i.e.*, DBS and transcript biomarkers) would reduce costs and consequently a higher number of tests from the same athlete over a prolonged period of time could be conducted. This improved monitoring would optimize the anti-doping system and deter doping (Figure 1).

The current detection methods for AAS and associated metabolites have improved in recent years, and the techniques of mass spectrometry (MS)-based analysis are able to identify long-term AAS metabolites in urine.[46] The improvement of the window of detection of some exogenous AAS (*e.g.*, dehydrochloromethyltestosterone and stanozolol) has been demonstrated in the re-analyses of samples that have been stored for anti-doping purposes since the 2004 Olympic Games. Seventy-four percent of the ADRVs of Olympic Games medal-winners from 1968 to 2012 were identified retrospectively, and 90% of those samples indicated AAS metabolites. Specifically, 79% of the detected substances were dehydrochloromethyltestosterone and stanozolol.[47] The most affected sports were athletics and weightlifting, and a study investigating the doping practices in weightlifting from 2008 to 2019 showed a doping practice marked by regional differences regarding the substances detected.[48] These findings benefit anti-doping systems by targeting certain regions for testing according to the prevalence of a given drug. Furthermore, advances in molecular biology technologies (*e.g.*, muscle memory analysis) can also aid in the detection of AAS doping in the long-term. More studies using gene expression analysis, especially with AAS users, can potentially identify gene expression signatures that could serve as biomarkers for long-term effects of AAS doping, with this system of testing as one of the pillars of the fight against doping.[49]

In addition to the detection of cheating athletes, there is now also the provision in the most recent revision of the WADA Code to sanction members of an athletes entourage that may be responsible for, or aided doping.[50] This essential amendment is envisaged to deter situations where doping is encouraged and facilitated by athlete support staff such as the revelations surrounding the Russian team doping scandal.[51] Another recent example relates to the high number of ADRVs of a specific AAS per country in the sport of international weightlifting. The prevalence of ADRVs for Stanozolol use was 60% in Romania and 51% in Kazakhstan, while Dehydrochloromethyltestosterone was 52% in Russia and Metandienone and EAAS were equally distributed in Thailand.[48] When examining the prevalence of certain types of substances in close geographical locations and especially within a country, there is an indication that systematic doping could be occurring. Therefore, there is an ever-increasing appetite for zero-tolerance of doping for athletes and all individuals involved in doping (*e.g.*, the athlete(s) entourage).

COVID-19 restrictions have also been accompanied by novel anti-doping methods as current anti-doping protocols are problematic as they impose serious risks of transferring the virus between the athlete and the anti-doping officer.[18] Recent research highlighted the original measures taken by some anti-doping organizations (*e.g.*, the US Anti-doping Agency) to combat the lack of anti-doping testing during the pandemic. These include athletes taking their own urine and dried blood samples at home (*i.e.*, in-home self-drug testing), supervised through videoconference, and sending these samples to the anti-doping laboratory.[52, 53] While this measure has resulted in some controversy,[54] its use may aid in more frequent doping testing in the future (Figure 1), which is one of the main issues as explained above.

An important development in the fight against doping has been the most recent revision of the WADA Code that stipulates that samples can be stored for up to 10 years after their initial analysis and retain the same legal rights if re-tested and prosecuted.[50] Arguably, long-term storage of samples represents one of the strongest deterrents of doping especially when there is a prospect of analysis using a variety of new methods as these are developed. Advances in anti-doping science are expected even if at too slow a rate given the lack of a concerted research effort and/or appropriate investment. WADA has committed US $80 million into scientific research since their formation. This funding support from WADA is much less than the transfer fee of one professional football player, such as Neymar (€220 million), Mbappé (€180 million), Philippe Coutinho (€145 million) and others. The research budget of WADA has also reduced considerably over the last 10 years with almost US $7 million (€5.7 million) spent in 2006 compared with US $1.5 million (€1.22 million) in 2018, a reduction of more than 78% in a 12-year period. Despite these impediments, research outcomes have enabled the detection of some drugs and metabolites that were not previously possible.[46] For example, an enzyme-linked immunosorbent assay (ELISA) was developed to detect the presence of Continuous EPO Receptor Activator (CERA) – an erythropoiesis-stimulating agent (EAS), and used in 2009 to reanalyze (for the first time) samples collected in the 2008 Beijing Games.[55] Similarly, despite much progress and potential to revolutionize anti-doping, the undisputed reality is that "omics" technologies have not been properly researched and tested hence anti-doping urgently needs serious investment for this purpose and therefore new partners. The need for a concerted "omics" research initiative in anti-doping is also evident by the recent award of the largest research grant ever made in the history of the Partnership for Clean Competition (PCC) ($1 million) for "omics" anti-doping research.[56, 57] This award and the "omics" results we (and others) have generated to date, in the context of what is happening in medical/disease diagnostics, confirm that it is only a matter of *when* rather than *if* "omics" methods will revolutionize anti-doping. Given these developments, long-term storage emerges as a major deterrent in the fight against doping, as cheating athletes and their accomplices will not feel safe knowing that they can be caught in the future.

Given the above promise, the inspirational speech of the IOC president, Thomas Bach, at the fifth WADA world conference in Katowice, Poland, and his pledge of $10 million for new anti-doping approaches with particular focus on genetic sequencing, DBS, and an ambitious long-term storage and re-analysis program, is destined to be game changing and a turning point in the fight against doping in sport and the protection of the clean athlete.[58] The underlying premise of the IOC president action plan was to increase the deterrence factor, and as such the IOC extended the storage time of samples and the subsequent reanalysis using new testing methods such as genetic sequencing as these became available. Specifically, the IOC has also initiated a global long-term storage and re-analysis program for samples collected during the pre-Games testing period. This means that these samples could also be stored for up to ten years, as the IOC already does for the samples taken during the Olympic Games. However, for this to happen, there is a need to revise the blood sample collection criteria set out by WADA to permit the use of tubes for stabilization of RNA. In summary, implementation of this very promising "game changer" detection method is expected to result in increased detection rates of blood doping without an increase in the cost of anti-doping. This outcome is expected to bring a culture change in terms of promoting clean competition.

Issues of classification in elite sport

Sport is historically designated by the binary categorization of male and female that conflicts with modern society (social identity) and the science of sex (biological traits). This contradiction, appreciated since antiquity, has come to the fore more recently with attempts to include transgender athletes and athletes with disorders of sex development (DSD) into elite sports.[59] From a performance standpoint, the main debate is the participation in elite sport of trans women athletes that have experienced puberty and development with testosterone concentrations in the male range, and female athletes with DSD that naturally have higher levels of endogenous testosterone.[60] The performance-enhancing role of testosterone is widely accepted in the literature[61] and the exposure to higher concentrations of testosterone is expected to provide a competitive advantage to trans women and DSD women athletes as argued by the International Sports Federation of World Rugby in their recent regulations that state that "*Transgender women may not currently play women's rugby*".[62] The banning of trans women athletes from elite rugby contrasts the previous International Olympic Committee (IOC) guidelines, that recommended the participation of trans women athletes in the female category if the athlete maintained their serum testosterone levels below 10 nmol/L for at least 12 months prior to competition.[63] The regulations by World Rugby are also contrary to those of World Athletics (International Association of Athletics Federations – IAAF, at that time), where testosterone levels in trans women athletes must not exceed 5 nmol/L continuously for a period of 12 months before competition.[64] The World Athletics regulations also determine the limit of 5 nmol/L of serum testosterone (for at least 6 months prior competition) for DSD women athletes in races from 400 m up to one mile.[64] A pertinent high-profile case is that of South African runner and two-time Olympic champion, Caster Semenya, who took her case to the Court of Arbitration for Sport (CAS) and lost her appeal against the regulations requiring her to undergo medical interventions to reduce her testosterone levels.[65]

How this complex situation resolves will depend on the balance between fairness, safety, and inclusion in sport. According to the Olympic Charter, "*The practice of sport is a human right*" and "*the rights and freedoms shall be secured without discrimination of any kind, such as race, colour, sex, sexual orientation, language, religion, political or other opinion, national or social origin, property, birth or other status*".[66] Each International Sports Federation is responsible for establishing their own rules to ensure equitable and fair competition, even when these rules are considered in opposition with the human rights of athletes to participate in sport, such as trans women rugby athletes and DSD women runners from 400 m to 1500 m. The decision by World Rugby to ban trans women from elite female competition was unsurprising given World Rugby prioritized *a priori* the safety of athletes over fairness and inclusion in deliberations.[62] Their main proceedings used by World Rugby to develop their guidelines for the inclusion of trans individuals within their sport were conducted with great transparency. Deliberations were conducted in public and arguments from both sides of the debate were published. Their primary premise was that the suppression of testosterone in trans women throughout a period of 12 months was nowhere near sufficient to offset the biological male advantages that pose a safety concern for female rugby players.[62] World Rugby argued that the remaining advantages in size, force- and power-production that are outcomes of high levels of testosterone in puberty in males, increase the risk of injuries in smaller and slower players during frequent collisions in the game.[62] However, World Rugby's arguments and evidence presented were not based on studies of trained athletes subject to gender affirming hormone treatment (GAT) – so the real physiological changes in trained transgender athletes remain unknown. The policy by World Rugby has been opposed by rugby unions such as England Rugby that will not implement the policy stating to the media that it "*believes further scientific evidence is required alongside detailed consideration of less restrictive measures in relation to the eligibility of transgender players*".[67] While World Rugby's guidelines and their assumptions using hypothetical modelling of elite male *versus* elite female athletes[62] may in time be proven correct, until data from longitudinal transgender athlete case-comparison studies that control for variations in hormonal exposure and involve numerous indices of performance become available, there is just as much circumstantial evidence to support this policy by World Rugby than there is to oppose it.

The World Athletics regulations have been challenged. In the Caster Semenya case previously described, the treatment to reduce her levels of testosterone is seem as a "*unnecessary medical intervention*" by the United Nations Human Rights Council[68] and the side effects of medications and the difficulties in maintaining serum testosterone levels below 5 nmol/L should be considered before proceeding.[69] Both the cases of DSD women and trans women athletes have the same limitations, the implementation of the regulations were based on a very limited number of studies carried out in non-specific populations. Meanwhile, the studies that have investigated the effects of testosterone levels and/or impact of GAT in trained trans women athletes are scarce. The discussion between experts on both sides of the argument to include/exclude DSD women and trans women athletes seems to be the best option moving forward. The 2021 consensus of the International Federation of Sports Medicine (*Fédération Internationale de Médécine du Sport* - FIMS) collected opinions from 70 authors regarding the inclusion of trans women and DSD female athletes in elite sport, that highlighted the need for innovative longitudinal research studies,[70] with specific athlete populations to generate the physiological and sport performance knowledge, that can be used as biomarkers for a fairer classification of athletes using more reliable biomarkers.[60]

Sport integrity issues related to technological advancements in sport

A pertinent and high-profile example of a sport integrity issue associated with the use of technology in sport are the ethical concerns linked to recent shoe technology developments. The use of carbon fiber plate (CFP) shoes have been shown to improve running economy by approximately 4%[71, 72] (and up to 6.4% in some cases),[73] and elite marathon times by 1.2% in males and 1.7% in females.[74] Since the introduction of this technology in 2016, world records in both male and female road running, from 5 km to the marathon have all been broken in CFP shoes.[75] From 2016 to 2020, CFP shoes were exclusively produced by a single shoe company, with non-sponsored athletes unable to access this technology and pushing some of these athletes to reject sponsorship from other companies limited to non-CFP shoes.[76] In the Rio Olympic marathon in 2016, all six medals were won by athletes wearing the same CFP shoe. Ironically, the winner of the women's race was also found positive for the PED erythropoietin a few months later;[77] illustrating the real magnitude of the combined integrity problem and the need for urgent resolution. Since then, 2020 has seen a number of shoe companies producing their own CFP shoes to allow their sponsored athletes compete under the same conditions.[75] Although nowadays most elite road runners are sponsored by shoe companies producing CFP shoes, recent records are distorted given that current shoe regulations (permission for using shoe prototypes during competitions, a maximum of 40 mm stack height and one CFP plate within the shoe) still have too large an impact on the energy cost of running, which require its revision to protect the essence of athletics and sport integrity.[78] The implementation of CFP spiked shoes to the track is also a reality since August 2020, when most athletes sponsored by a well-known company wore CFP spikes during the 2020 Diamond League in Monaco. The first CFP spiked prototypes were designed for middle- and long-distance track events (*i.e.*, from 800 m to 10000 m) and long-standing world records (*e.g.*, 5000 and 10000 m) were broken just a few months after their introduction. New spiked prototypes are currently under development for sprinting events (*i.e.*, from 60 m to 400 m), raising further concerns that current track world records might follow the same pattern as all the road records, including the 100 m and 200 m world records by Usain Bolt.

Like with other integrity issues dealt with in this review, it is the responsibility of the International Sports Federations to oversee the development of rules to safeguard the integrity of their respective sport and competition. The rules (*i.e.*, Rule 143, Shoes) when the CFP shoes made their appearance in the Rio Olympic marathon where all six medals were won by athletes wearing the same CFP shoe, stated "The purpose of shoes for competition is to give protection and stability to the feet and a firm grip on the ground. Such shoes, however, must not be constructed so as to give an athlete any unfair additional assistance, including the incorporation of any technology which will give the wearer any unfair advantage".[79] There was no further iterations of the rules until the update of the same rule in 2018-2019 that stated: "Such shoes, however, must not be constructed so as to give athletes unfair assistance or advantage. Any type of shoe used must be reasonably available to all in the spirit of the universality of athletics."[80] In January 2020, World Athletics reacted to the enormous controversy in shoe technology by announcing new rules stating that sole thickness of a marathon shoe must not exceed 40 mm (25 mm for spiked shoes) and must be on sale for at least four months before they can be used in competition.[78] A positive step of these new rules in terms of sporting integrity was the requirement for a shoe to be "openly available to all" and if not "then it will be deemed a prototype and use of it in competition will not be permitted". However, near the end of 2020, World Athletics announcing that prototypes would be permitted in most World Athletics-sanctioned events but not the Olympics or at any World Athletics Series events (which are any world championships, the World Athletics Continental Cup or the World Athletics Relays).[81] The revised rules state that the "development shoes", named this way as they are meant to give shoe manufacturers a year-long window to test their products in race situations and continue to develop their technologies, "can only be worn for up to 12 months" before being made available to the public. The logic of this update is beyond the scope of this review,[81] but this rule permitting prototypes raises serious practical problems such as enforcement of the rule (*e.g.*, need to have access to MRI/CT scanners at athletic events). World athletics have stated that they reserved the right to examine a sample of any athlete's shoes and, if necessary, cut it open to ensure the shoe complies with the rules.[81]

The sports integrity issue surrounding the "legality" and "ethics" of CFP shoes is not unprecedented. In 2009, the International Swimming Federation (FINA) chose under pressure from the controversy to modify the rules and ban full-body swimsuits in response to numerous sudden world records broken by swimmers wearing this technology.[82] Even World Athletics (then IAAF) faced their own technological issue with shoe designs in the 1960s where both the 200 and 400 m world records were broken within the space of two weeks in 1968, with both athletes wearing the newly developed "brush" shoe.[83] On that occasion, the governing body of athletics chose to expunge the records broken with these shoes after the advantage of this technology was later confirmed in a study that reported improvements in running performance in five out of six athletes tested.[84] These complex and multifactorial issues related to the implementation of new innovative technology is not only an issue for the sport of athletics but all International Sports Federations who have their own technology concerns to address and how this latest integrity issue is resolved will have a far-reaching implications.

Conclusions

The major integrity challenges previously facing competitive sport have been accentuated further during COVID-19. The existential threats to the integrity of sporting competition reside in all forms of traditional doping, issues of technological fairness, and integration of transgender and intersex athletes in elite sport. While the enforced lull in competitive sport has provided an unprecedented opportunity for stakeholders in sport to focus on unresolved integrity issues and develop and implement long-lasting solutions, there is a need to embrace the many technological innovations that have accelerated and been perfected during COVID-19 that will enable us to emerge stronger from this pandemic. Committed engagement with all available technology including 'omics' technology, big data, bioinformatics and machine learning/artificial intelligence approaches will be needed to modernise sport and resolve the major integrity issues facing elite sport.

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