**TITLE: Three seasons of enhanced safety surveillance of a cell culture-based quadrivalent influenza vaccine**

**RUNNING TITLE: Enhanced safety surveillance of Flucelvax Tetra**

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**Data availability statement**

All relevant data are within the manuscript and associated supporting information.

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**Conflict of interest disclosure**

Maria Piedrahita-Tovar is a full-time employee of CSL Seqirus, a pharmaceutical company that manufactures and markets influenza vaccines, including Flucelvax® Tetra. Alexander Domnich was previously a full-time employee of Seqirus s.r.l. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Ethics approval statement**

Protocols for the EPSS activity were approved by the Ethics Committee of Liguria Region (resolutions 222/2019 and 346/2020).

**Patient consent statement**

The decision to vaccinate is part of routine clinical care and the choice of vaccine type or brand is solely at the discretion of the vaccinating physicians. General practitioners obtained informed consent for vaccination from all subjects.

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Not applicable.

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**Abstract**

**Background:** Enhanced safety surveillance (ESS) of seasonal influenza vaccines is required by the European Medicines Agency (EMA). ESS is conducted during each Northern Hemisphere (NH) influenza season and aims to monitor the reactogenicity of influenza vaccines early in the season. A cell culture-based quadrivalent influenza vaccine (QIVc; Flucelvax® Tetra), which has an advantage of avoiding egg-adaptive mutations that may reduce vaccine effectiveness, has been available in Europe since the 2019/20 influenza season. The objective of this manuscript is to summarize ESS activity across three seasons for QIVc in all age groups.

**Methods:** As per EMA guidelines, an enhanced passive safety surveillance (EPSS) approach was adopted. The EPSS envisages near-real-time surveillance of adverse events (AEs) that are reported spontaneously by vaccinees. The EPSS was conducted in primary care setting in Genoa (Italy) during the seasons 2019/20, 2020/21 and 2021/22. All AEs registered within the first 7 days following immunization were analyzed by season, type, age group and seriousness.

**Results:** Over three seasons, a total of 3,603 QIVc exposures were recorded within EPSS. No safety signals were identified. The overall reporting rates of individual case safety reports (ICSRs) for the seasons 2019/20, 2020/21 and 2021/22 were 1.75% (18/1030), 0.48% (5/1032) and 0.40% (4/1001), respectively. The average number of AEs per ICSR was similar (range 3.3–3.8) across the three seasons. Most AEs were reactogenic in nature. The rate of AEs was similarly low in all age groups.

**Conclusions:** These results support the favorable safety profile of QIVc in all indicated age groups.

**Keywords**

Influenza, cell-based influenza vaccine, Flucelvax® Tetra, enhanced safety surveillance, safety; adverse event

1. **Introduction**

Seasonal influenza is responsible for a large global burden of disease, with approximately one billion cases each year, of which 290,000–650,000 result in death.1 Influenza vaccination is an important public health means for reducing the global burden of disease.2 Pregnant women, young children, older adults, subjects with underlying medical conditions and healthcare workers (HCWs) have been identified1 as principal target populations for annual immunization.

The currently available seasonal influenza vaccines (SIVs) differ by several characteristics, including virus inactivation patterns (live attenuated, inactivated split virion or subunit), antigen content (standard dose of 15 *µ*g per strain vs high dose of 60 *µ*g per strain) and presence or absence of adjuvants. In the United States (US) 3 and most European countries like Italy,4 all the above-described SIVs are quadrivalent (QIV), containing two influenza A strains A(H1N1)pdm09 and A(H3N2) and two B strains belonging to lineages Victoria and Yamagata. While most QIVs are still produced in eggs, recent advances have brought alternative egg-free production platforms, such as cell culture and recombinant technologies.5 Advantages of these technologies include a lack of reliance on large-scale egg supply, scalability and use of closed-system bioreactor manufacturing processes that reduce risk of contamination.6 However, the most important benefit of the cell-based SIVs is the prevention of egg-adaptive mutations, which can arise during serial egg passages.7 Egg-adaptive mutations frequently alter vaccine antigenicity properties8 and have been proposed to be an important driver of the suboptimal SIV effectiveness, especially against influenza A(H3N2).8,9 The available systematic evidence suggests10 that in some seasons cell-based QIVs may be more effective than egg-based QIVs.

Contrary to other pharmaceuticals, vaccines are mostly given to large numbers of healthy individuals and therefore continuous post-marketing monitoring of their safety is essential.11 SIVs have at least three distinctive features compared to other vaccines: (i) their formulation may change every season (up to twice a year) to keep pace with the evolving virus population; (ii) SIV campaigns take place in a well-defined and relatively short time window12 and (iii) availability of several SIV brands3,4 utilizing different manufacturing technologies, which may have different safety profiles.13 These aspects further enhance the need for near-real-time safety surveillance activities to be able to rapidly identify safety signals and enable re-assessment of SIV benefit–risk. In this regard, the European Medicine Agency (EMA) has issued14 requirements for annual enhanced safety surveillance (ESS) to be performed throughout the post-marketing life cycle of approved SIVs in the European Union (EU).

In Italy, a cell culture-based QIV (QIVc; Flucelvax® Tetra, Seqirus Inc, Summit, NJ, USA) has been available since the 2019/20 influenza season.15 Despite several phase III randomized clinical trials have suggested a good safety profile of QIVc, which is similar to standard egg-based SIVs,16 no ESS data for QIVc has been available. The objective of this paper is to summarize ESS activity across three seasons (from 2019/20 to 2021/22) for QIVc in all age groups.

1. **Methods**
   1. **Overall surveillance design and setting**

The ESS was coordinated by the Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT; Genoa, Italy), which is an interregional influenza surveillance network, and was conducted in the metropolitan city of Genoa (Italy). The interim guidance issued by EMA14 outlines three options for carrying out ESS, namely active surveillance, passive surveillance, and data mining/use of electronic record data. The choice among the three options should be justified and agreed with the EMA or relevant local competent authorities. Accordingly, CSL Seqirus included enhanced passive safety surveillance (EPSS) in its routine pharmacovigilance activities. Some of the benefits of the data collection through the EPSS are: (i) increased vaccinee’s awareness of reporting AEs; (ii) facilitation of the reporting by providing vaccinees with contact information for signaling AEs and (iii) improvement of quality of the individual case safety reports (ICSRs).17 In Europe, the EPSS approach has been adopted for other SIVs, including MF59-adjuvanted subunit,17 split virion standard-dose18-21 and high-dose20 formulations.

This report describes results of the EPSS conducted during three consecutive NH influenza seasons (2019/20, 2020/21 and 2021/22). The EPSS protocol was compliant with the interim EMA guidelines .14 For each season, we aimed to include at least 1,000 routine exposures to QIVc, which is a commonly used sample size in EPSS.17-21 In particular, by vaccinating 1,000 individuals, the cumulative Poisson law probability of observing at least one AE is > 99.9%.

EPSS is a routine pharmacovigilance activity, as the decision to vaccinate is part of routine clinical care and the choice of SIV type or brand (including QIVc) is solely at the discretion of the vaccinating physicians. Protocols for the EPSS activity were approved by the Ethics Committee of Liguria Region (resolutions 222/2019 and 346/2020).

* 1. **Exposure to the cell culture-based quadrivalent influenza vaccine (QIVc)**

QIVc is an inactivated non-adjuvanted standard-dose (15 *μ*g of hemagglutinin per strain) subunit vaccine that contains surface antigens (hemagglutinin and neuraminidase) of four strains, which are regularly updated according to the World Health Organization’s (WHO) recommendations for the NH season.22 In particular, during the surveillance period of three consecutive seasons both the A(H1N1)pdm09 and A(H3N2) strains changed each year. B/Victoria vaccine strain changed for the 2020/21 season, whilst the B/Yamagata QIVc strain remained unchanged for all three seasons (Table S1). QIVc is manufactured from influenza viruses propagated in the Madin-Darby canine kidney (MDCK) cell culture. Vaccinees were enrolled according to the age indication of QIVc, which for the 2021/22 season changed from adults and children ≥ 9 years to adults and children ≥ 2 years.

During the three seasons, 13–14 general practitioners (GPs) and primary care pediatricians routinely administered QIVc at their practices. Before the start of each vaccination campaign, all physicians were trained on all relevant aspects of the EPSS. Following immunization, each vaccinee or his/her legal representative were encouraged to report any AE in general and, in particular, those occurring in the first 7 days. To facilitate spontaneous reporting, each vaccinee was provided with a standardized and uniquely numbered vaccination card that reported SIV brand (Flucelvax® Tetra) and associated batch number, date of vaccination and contact details to report AEs. The number of vaccination cards distributed corresponds to the total exposure (denominator for the reporting rate calculation).

* 1. **Data collection and analysis**

The ICSRs was created when ≥ 1 AE was reported for a vaccine recipient and served as the primary source data. ICSRs were collected and processed by trained personnel at a toll-free call center, the phone number for which was provided on vaccination cards, through a structured standardized interview. This interview aimed to systematically collect the following information: verbatim description of the AEs experienced, their onset, severity and outcome, vaccination card number, vaccinee’s demographics, past and present health-related conditions, and concomitant medications.

For the purpose of EPSS, each ICSR had to meet the following eligibility and validity criteria: (i) reported to the call center within the EPSS activity; (ii) AE occurrence within the first 7 days post-vaccination; (iii) ≥ 1 identifiable reporter; (iv) ≥ 1 identifiable vaccine recipient; (v) ≥ 1 suspected AE; (vi) ≥ 1 suspected vaccine. Ineligible ICSRs were excluded from the EPSS analysis but were included in the continuous routine surveillance of QIVc data in the CSL Seqirus global safety database.

Vaccinee’s reported verbatim text was translated into English and coded to the preferred terms (PTs) using the current (at the time of each seasonal EPSS) version of the Medical Dictionary for Regulatory Activities (MedDRA). ICSRs were then reviewed by the CSL Seqirus Pharmacovigilance and Risk Management Team according to standard good pharmacovigilance practice.23

The AEs received within EPSS were analyzed and classified as reactogenic AEs of interest (rAEIs), events of interests monitored for the periodic safety update reports (PSUR) or other events. rAEIs included systemic events, such as fever, nausea, vomiting, malaise, headache, decreased appetite, myalgia, arthralgia, irritability and crying (for children aged < 5 years), injection site reactions such as pain, erythema, induration and swelling, and events indicative of allergic and hypersensitivity reactions (including rash and ocular symptoms). All AEs were also classified by seriousness (serious vs non-serious). Serious AEs were defined as those that resulted in death, persistent or significant disability or incapacity, were life-threatening or required hospitalization. Frequency of AEs was described overall, by their seriousness and age groups (2-8/9–17, 18–64 and ≥ 65 years of age) and compared with their expected frequency, as per the summary of product characteristics (SmPC) of QIVc.24

* 1. **Statistical analysis**

Rates of ICSRs and individual AEs of interest were reported as percentages with exact Clopper-Pearson’s 95% confidence intervals (CIs). Fisher’s exact test was used to compare reporting rates across the seasons. The exact binomial test was used to test the null hypothesis of the equal sex distribution of ICSRs. Statistical analysis was performed in R stats packages v. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

1. **Results**

Distribution of vaccination cards coincided with the beginning of national immunization campaigns and most doses were administered between mid-October and November of each season. As per protocol, in each season at least 1,000 vaccination cards were distributed, and most exposures occurred in working-age adults (Table 1).

The overall frequency of ICSRs diminished (*p* = 0.002) over time with reporting rates of 1.75% (18/1030), 0.48% (5/1032) and 0.40% (4/1001) documented during the NH seasons 2019/20, 2020/21 and 2021/22, respectively. However, in the 2019/20 season, 8 out of 18 ICSRs did not meet the eligibility criterion of the availability of a unique identification number of the vaccination card and were therefore excluded. Characteristics of the excluded ICSRs are reported in Table S2.

Most ICSRs concerned working-age adults. Conversely, during the three seasons there was only one ICSR registered in the pediatric age-class (Table 2). With regard to sex, most (84.7%, 16/19; *p* = 0.004) ICSRs were reported for women, especially during the first two seasons (2019/20: 9/10; 2020/21: 5/5; 2021/22: 2/4).

The average number of AEs (any AE) per ICSR analyzed was similar across the three seasons (2019/20: 3.5, 35/10; 2020/21: 3.8, 19/5; 2021/22: 3.3, 13/4) and most of these were considered rAEIs. As shown in Table 3, the most common systemic rAEIs were fever, malaise and headache, while injection site swelling and erythema were the most common local rAIEs.

Two ICSRs were likely to be hypersensitivity reactions. The first occurred in a 43-year-old female who reported dry mouth, tongue erythema and a stretching sensation around her mouth (coded as oral discomfort) a few hours after being administered QIVc, all judged non-serious. No systemic allergic AEs were reported. From the reported medical history, the patient was allergic to some foods and recalled experiencing a similar sensation after previous episodes of food allergy. The patient recovered from all events within 12 hours. The causality assessment was confounded by food the patient ate that day. The second ICSR was reported by a consumer (neither patient nor HCW) and regarded a woman of unknown age who developed an allergic reaction (swollen tongue, lip swelling, swelling face, dyspnea, tachycardia, vomiting, hand erythema, cold sweats, tinnitus and paresthesia) approximately one hour after exposure to QIVc. From her past history, she had undergone surgery for metastatic thyroid cancer and at the time of QIVc receipt was on levothyroxine replacement treatment. The patient had never been vaccinated with SIV. Following sublingual administration of betamethasone sodium citrate, her symptoms started to abate and the patient was transferred to an emergency department, where the corticosteroid therapy was continued. The patient recovered from all events on the same day. This event was judged serious and related to QIVc.

When analyzed by age group, all rates of all rAEIs were below the corresponding expected rates (Tables S3–S5).

Other AEs were less frequently reported than rAEIs and the reporting rate of single AEs did not exceed 0.2% (Table S6). There were two cases, both judged serious, identified by the MedDRA PT as “Influenza”. In the context of symptom onset of one and two days after QIVc administration, respectively, vaccination failure was not biologically plausible as insufficient time had passed for a complete immune response to develop, and the reported events were likely ascribable to influenza-like symptoms.

The proportion of serious AEs was 11.4% (4/35), 26.3% (5/19) and 30.8% (4/13) for the 2019/20, 2020/21 and 2021/22 seasons, respectively (*p* = 0.24). None of the serious AEs were life-threatening or fatal.

Finally, given a significant proportion of non-valid ICSRs (*n* = 8) registered during the 2019/20 season, we conducted a *post-hoc* sensitivity analysis, in which these ICSRs were included (Table S7). The overall number of AEs increased by 65.7% (from 35 to 58) and this increase regarded mostly rAEIs like fever, malaise (from 0.29% to 0.49% for both), malaise and injection site pruritus (from 0.10% to 0.29%). However, all AEs were constantly below the expected rates (< 0.5% for all).

1. **Discussion**

This EPSS activity supports24 a favorable safety profile for QIVc, which was consistent across the three seasons and all age groups. Spontaneous surveillance activities like EPSS14 have the main aim of safety signal detections and hypothesis generating. Although different in nature, the US Vaccine Adverse Event Reporting System (VAERS)25 was able to successfully identify a safety signal of febrile seizures in young children vaccinated with an egg-based trivalent SIV.26-27 The present EPSS did not identify any safety signal that could alter the benefit-risk profile of QIVc.

Most AEs reported were judged reactogenic in nature and non-serious, which is in line with both the current SmPC24 and data from QIVc clinical development (reviewed in 28). Analogously, active post-marketing surveillance of the safety of QIVc administered to Italian HCWs (*n* = 775) during the 2019/20 influenza season29 documented only one (0.13%) serious AE, which was judged unrelated to QIVc.

Compared with more recent 2020/21 and 2021/22 seasons, the overall AE reporting rate was significantly higher during the 2019/20 influenza season. A similar trend was observed in the Italian monitoring system of AEs following vaccination with any available SIV: from 2019/20 to 2020/21 the overall reporting rate dropped from 2030 to 3.931 per 100,000 doses administered. In the same manner, EPSS of an egg-based QIV noted a two-fold decrease (from 5.96% to 2.88%) in the ICSR reporting rate from 2019/20 to 2020/21.21 It is therefore likely that this decrease was not driven by changes in the safety profile of QIVc or any other SIV, but rather was due to the external influence of the COVID-19 pandemic. On the other hand, it appears that the COVID-19 pandemic had an impact on reporting only non-serious AEs. Indeed, although non-significant (*p* = 0.24) for a small number of cases, we observed a relative increase in the proportion of serious AEs, which was in countertrend to the overall reporting. In this regard, the above-mentioned Italian vaccinovigilance platform reported31 a stable notification rate of serious AEs, suggesting a higher population awareness to report this type of events. Furthermore, a comprehensive time-series analysis of the Pfizer’s safety database (700,362 spontaneous reports of all Pfizer’s medicines) has demonstrated that the overall decline in reporting observed during the first pandemic waves was country-specific and driven mainly by HCWs (as opposed to consumers) and non-serious AEs.32

Across the three seasons, most AEs were reported by female vaccinees. Overall, it seems that women are involved in more AE reporting, especially for non-serious AEs (reviewed in 33,34). It has been estimated35 that approximately 70% of all (*n* = 15,871) VAERS reports on SIVs submitted between 1 December 1, 2020 and October 8, 2021 regarded women. This gender-related gap may be explained by a true increase in the reactogenicity of SIVs in women, but more likely, by a higher propensity of females to report AEs.33-34 Taken together, these data indicate that healthcare professionals should put an extra effort on raising awareness of reporting AEs following vaccination of men.

The main inherent limitation of the EPSS is that AEs are reported spontaneously (and not gathered actively) and therefore are subject to some under-reporting. On the other hand, vaccinees taking part in EPSS were encouraged by their GPs to signal all AEs, which is expected to have increased the overall reporting rate. Indeed, during the 2019/2030 and 2020/2131 influenza seasons, the rates of AEs following any marketed SIV reported by the Italian Medicines Agency were 20 and 3.9 per 100,000 doses, respectively. The corresponding frequencies established in the current EPSS were 88 (1,750 per 100,000 doses) and 123 (480 per 100,000 doses) times higher for the 2019/20 and 2020/21 seasons, respectively. Another shortcoming is the lower exposure to QIVc of the pediatric population, especially during the 2019/20 season. This, however, reflects a very low influenza vaccination coverage rate among Italian children.36

In conclusion, this EPSS of AEs following vaccination with QIVc did not identify any safety signal and confirmed the favorable safety profile of QIVc in both the pediatric and adult populations. EPSS is a feasible safety signal detection method that can be conducted on the annual basis.

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**TABLE 1** Overall exposure to the cell culture-based quadrivalent influenza vaccine (QIVc), by age group and season

|  |  |  |  |
| --- | --- | --- | --- |
| **Age group, years** | **Influenza Season, *n* (%)** | | |
| **2019/20** | **2020/21** | **2021/22** |
| 2/9–17a | 95 (9.22) | 214 (20.74) | 257 (25.67) |
| 18–64 | 652 (63.30) | 577 (55.91) | 502 (50.15) |
| ≥ 65 | 283 (27.48) | 241 (23.35) | 242 (24.18) |
| Total | 1030 (100) | 1032 (100) | 1001 (100) |

a9–17 years for the seasons 2019/20 and 2020/21 and 2–17 years for the influenza season 2021/22.

**TABLE 2** Number and reporting rates of illegible individual case safety reports (ICSRs) in subjects immunized with the cell culture-based quadrivalent influenza vaccine (QIVc), by age group and season

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age group, years** | **Frequency of individual case safety reports in each season** | | | | | |
| **2019/20** | | **2020/21** | | **2021/22** | |
| ***n*/*N*** | **% (95% CI)** | ***n*/*N*** | **% (95% CI)** | ***n*/*N*** | **% (95% CI)** |
| Any | 10/1030 | 0.97 (0.47–1.78) | 5/1032 | 0.48 (0.16–1.13) | 4/1001 | 0.40 (0.11–1.02) |
| 2/9–17a | 0/95 | 0 (0–3.81) | 1/214 | 0.47 (0.01–2.56) | 0/257 | 0 (0–1.43) |
| 18–64 | 8/652 | 1.23 (0.53–2.40) | 2/577 | 0.35 (0.04–1.25) | 2/502 | 0.40 (0.05–1.43) |
| ≥ 65 | 2/283 | 0.71 (0.09–2.53) | 0/241 | 0 (0–1.52) | 2/242 | 0.83 (0.10–2.95) |
| Unknown | 0/1030 | 0 (0–0.36) | 2/1032 | 0.19 (0.02–0.70) | 0/1001 | 0 (0–0.37) |

a9–17 years for the influenza seasons 2019/20 and 2020/21 and 2–17 years for the influenza season 2021/22

**TABLE 3** Number and reporting rates of reactogenic adverse events of interest in individuals of all ages immunized with the cell culture-based quadrivalent influenza vaccine (QIVc), by season

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Type** | **Reactogenic adverse event of interest** | **2019/20 (*N* = 1030)** | | **2020/21 (*N* = 1032)** | | **2021/22 (*N* = 1001)** | |
| ***n*** | **% (95% CI)** | ***n*** | **% (95% CI)** | ***n*** | **% (95% CI)** |
| Systemic | Fever | 3 | 0.29 (0.06–0.84) | 1 | 0.10 (0.00–0.54) | *1* | *0.10 (0.00–0.56)* |
| Nausea | 2 | 0.19 (0.02–0.70) | 0 | 0 | 0 | 0 |
| Vomiting | 1 | 0.10 (0.00–0.54) | *1* | *0.10 (0.00–0.54)* | 0 | 0 |
| Malaise | 3 | 0.29 (0.06–0.84) | 0 | 0 | 1 | 0.10 (0.00–0.56) |
| Headache | 3 | 0.29 (0.06–0.84) | 0 | 0 | 0 | 0 |
| Decreased appetite | 0 | 0 | 0 | 0 | 0 | 0 |
| Myalgia | 0 | 0 | 0 | 0 | 0 | 0 |
| Arthralgia | 0 | 0 | 0 | 0 | *1* | *0.10 (0.00–0.56)* |
| Irritability/crying | 0 | 0 | 0 | 0 | 0 | 0 |
| Local | Pain | 2 | 0.19 (0.02–0.70) | 0 | 0 | 0 | 0 |
| Erythema | 1 | 0.10 (0.00–0.54) | 1 | 0.10 (0.00–0.54) | 1 | 0.10 (0.00–0.56) |
| Induration | 0 | 0 | 1 | 0.10 (0.00–0.54) | 0 | 0 |
| Swelling | 3 | 0.29 (0.06–0.84) | 1 | 0.10 (0.00–0.54) | 1 | 0.10 (0.00–0.56) |
| Allergic | Hypersensitivity | 0 | 0 | *1a* | *0.10 (0.00–0.54)* | 0 | 0 |
| Swollen face | 0 | 0 | *1a* | *0.10 (0.00–0.54)* | 0 | 0 |
| Lip swelling | 0 | 0 | *1a* | *0.10 (0.00–0.54)* | 0 | 0 |
| Swollen tongue | 0 | 0 | *1a* | *0.10 (0.00–0.54)* | 0 | 0 |
| Dry mouth | 0 | 0 | 1b | 0.10 (0.00–0.54) | 0 | 0 |
| Tongue erythema | 0 | 0 | 1b | 0.10 (0.00–0.54) | 0 | 0 |
| Oral discomfort | 0 | 0 | 1b | 0.10 (0.00–0.54) | 0 | 0 |
| Rash | 0 | 0 | 0 | 0 | 0 | 0 |
| Pruritus | 1 | 0.10 (0.00–0.54) | 0 | 0 | 0 | 0 |

Abbreviation: rAEI, reactogenic adverse event of interest.

aAll events occurred in the same individual A; bAll events occurred in the same individual B. Serious adverse events are evidenced *in italics*. Upper limit of the exact 95% confidence interval for zero events is 0.36 for the influenza seasons 2019/20 and 2020/21 and 0.37 for the season 2021/22.