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RESEARCH ARTICLE

Isolation Protocols for Mitigate Influenza in Children

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ABSTRACT

Objective: Influenza, which is characterized by febrile nature and acute respiratory manifestations, poses a significant threat to children with respect to morbidity and mortality. This study aimed to assess influenza infection data among children during periods of enforced isolation and subsequently when these measures were lifted.

Methods: This retrospective cross-sectional study categorized patients into two groups: i) influenza direct fluorescent antibody test (DFT) positive patients admitted between June 16, 2021 and June 15, 2022, when isolation measures were in effect (Group 1) and ii) influenza DFT-positive patients admitted between June 16, 2022 and June 15, 2023, when isolation measures were lifted (Group 2).

Results: Influenza A was predominant in Group 1, whereas influenza A and B were more evenly distributed in Group 2, demonstrating a statistically significant difference ($p<0.001$). The incidence of moderate-to-severe disease was significantly higher in Group 2 than in Group 1 ($p<0.001$). Groups 1 and 2 differed significantly in terms of hospitalization duration and clinical recovery time (5 [1–7] days vs. 7 [3–9] days, **$P<0.001$ and 3 [1–4] days vs. 5 [4–7] days, $p<0.001$, respectively). The analysis of monthly infection distribution revealed a peak occurring 3 months earlier in Group 2 than in Group 1. In Group 1, compliance rates to vaccination recommendations by physicians and pediatricians were 33% and 58%, respectively, whereas compliance rates in Group 2 were 31.5% and 43.7%, respectively.

Conclusions: Implementing basic measures such as hand hygiene and mask-wearing can mitigate viral outbreaks. Elevating the rate of physician-recommended vaccinations can potentially alleviate disease burden and mitigate disease severity.

Keywords: Oseltamivir, Influenza, Isolation, Vaccine, SARS-CoV-2

INTRODUCTION

Influenza is an acute respiratory illness in children that is primarily attributed to influenza A and B viruses. Although it typically manifests as a self-limiting and uncomplicated condition, it cyclically precipitates global epidemics, particularly during the winter months, occasionally leading to morbidity and mortality in children (1). The World Health Organization has underscored the magnitude of seasonal influenza, estimating 1 billion cases annually, with 3–5 million patients experiencing severe disease (2).

Antiviral drugs, particularly oseltamivir, are essential in treating influenza infections. Oseltamivir is recommended because of its ability to reduce symptoms and shorten illness duration in children. It is recommended for serious, complicated, or progressively worsening cases possibly or definitely caused by influenza, irrespective of the influenza vaccination status, with initiation within the first 48 hours of illness (3, 4). The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices and the American Academy of Pediatrics advocate universal annual influenza vaccination for children aged >6 months, barring contraindications preceding the onset of influenza activity in the community (3, 5).

Considering the coronavirus disease 2019 (COVID-19) pandemic that began in 2020, global isolation measures, such as face mask use, hand hygiene, and social distancing, were implemented. In Turkey, schools were closed between September 2021 and

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September 2022 with mandatory mask use and strict isolation measures. September 2022 marked the reopening of schools, the ease of isolation measures, and the start of a return to normalcy. This study examined influenza infection data in children in 2021–2022 when isolation measures were in force and 2022–2023, following relaxation. The primary objective was to assess the impact of lifting isolation measures on influenza infection among children, while the secondary objective was to examine post-pandemic vaccination attitudes.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at a tertiary academic hospital in Istanbul, Turkey, and included patients aged 18 years who were admitted to the pediatric inpatient unit between June 16, 2021 and June 15, 2023. The patient cohort was selected from the hospital's information system using the test entry code for the Influenza Direct Fluorescent Antibody Test (DFT). DFT is an antigen detection method in which viral proteins within infected cells are stained with fluorophore-linked antibodies and visualized under a fluorescence microscope (6). A meta-analysis reported sensitivities of 80.0% for influenza A and 76.8% for influenza B, with a specificity exceeding 98% for the DFT (7).

Patients were categorized into two distinct groups: i) influenza DFT-positive individuals admitted between June 16, 2021, and June 15, 2022, corresponding to the period of isolation measure implementation (Group 1) and ii) influenza DFT-positive individuals admitted between June 16, 2022, and June 15, 2023, subsequent to the easing of isolation measures (Group 2). The selection of the current dates during the comparison of years is attributed to the lifting of measures in June 2022 and the structuring of a school year spanning September to June. Consequently, both years encompassed the influenza season.

In the year of isolation measure implementation, influenza DFTs were submitted by 2540 patients, whereas in the year following the relaxation of isolation measures, 3086 patients submitted influenza DFTs, with a total of 712 patients testing positive for influenza. However, 26 patients were excluded from the study due to missing data. Thus, Group 1 included 292 patients and Group 2 included 394 patients.

The two groups were compared regarding various parameters, including the distribution of admission dates, age (in months), sex, presenting complaints and clinical findings, underlying medical conditions, rate of influenza A/B positivity, incidence of concomitant viral infections, laboratory values, hospitalization rates, treatment status, duration of hospital stay, duration of clinical recovery, rate of moderate to severe disease manifestation, utilization of respiratory support, and vaccination status. The comparison was extended to individuals exhibiting mild and moderate-to-severe disease, with evaluations encompassing age (in months), gender, rate of influenza A/B positivity, underlying medical conditions, and co-infection rates.

Antigen detection using DFT was performed to identify adenovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and respiratory syncytial virus (RSV). Patients exhibiting significant dyspnea at rest, mental status alterations, clinical deterioration related to hypoxemia, impaired oral intake, and severe complications, such as secondary bacterial pneumonia, as well as those needing mechanical ventilator support were categorized as having moderate to severe disease. The duration of clinical improvement was defined as the period between the initial day of reduced oxygen therapy and the onset of respiratory symptom regression. In Turkey, comprehensive records of citizens' vaccination histories are systematically documented within the national electronic personal health system operated by the Ministry of Health, known as "enabız.gov.tr." This secure platform is accessible to healthcare professionals through a secure login system. The vaccination status of patients was corroborated through two distinct methods: i) verbal declarations provided by parents and ii) cross-referencing with the information available in the national electronic personal health system (enabız.gov.tr). The rate at which physicians recommend vaccines to families was derived from the hospital information notes.

Statistical analysis was conducted using SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The Shapiro–Wilk test was used to determine the normal distribution of variables. Descriptive statistics were employed to present variables, with categorical variables expressed as numbers and percentages and numerical variables presented as mean, standard deviation, median, 25th percentile, and 75th percentile. The chi-square test, Student's t-test, and Mann–Whitney U test were used to compare categorical and numerical variables between the two groups, depending on the sample distribution. Statistical significance was set at $p<0.05$.

RESULTS

During the period of isolation measures, 305 out of 2540 children (12%) tested positive for influenza, whereas in the year when isolation measures were lifted, 407 out of 3086 children (12.7%) were found to be positive for influenza (p=0.428). The study was conducted on 686 patients (292 in Group 1 and 394 in Group 2) after excluding 26 patients whose data were unavailable. The distribution of patients according to the date of influenza diagnosis is shown in Figure 1. More than half of the patients were male, with a median age of 40 (13–89.75) months. In Group 1, comprising 53.4% males, the median age was 34 (7–83) months, while in Group 2, with 56.6% males, the

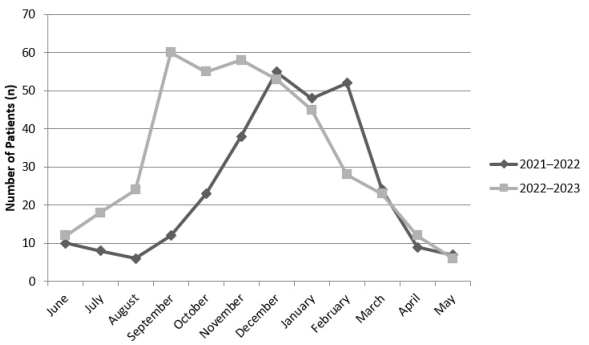

Figure 1: Influenza infection dates of the patients.

median age was 44.5 (16–93.2) months (p=0.408 and p=0.004, respectively). Forty patients (5.8%) tested positive for influenza A and B viruses. Table 1 presents data on patient complaints, examination findings, comorbidities, co-infections, laboratory values, hospitalization status, and respiratory support.

Comparison of Group 1 and Group 2 regarding the duration of hospitalization and clinical recovery time revealed a statistically significant difference (5 [1–7] days vs. 7 [3–9] days, p<0.001 and 3 [1–4] days vs. 5 [4–7] days, p<0.001, respectively).

Group 1 included 267 (91.4%) cases of mild disease and 25 (8.5%) cases of moderate to severe disease, whereas Group 2 included 314 (79.7%) mild and 80 (20.3%) moderate to severe cases, indicating a statistically significant difference (p<0.001). Of all patients, only one fatality occurred (in Group 2). The

Table 1. Patients' complaints, examination findings, comorbidities, co-infections, laboratory values, hospitalization status, treatment, and respiratory support

		Total n (%)	Group 1 n (%)	Group 2 n (%)	p ¶
Influenza A		546 (79.6)	287 (98.2)	259 (65.7)	**<0.001**
Influenza B		180 (26.2)	17 (5.8)	163 (41.4)	**<0.001**
Complaints	Fever	492 (71.7)	185 (63.4)	307 (77.9)	**<0.001**
	Cough	327 (47.7)	151 (51.7)	176 (44.7)	0.073
	Nasal discharge	85 (12.4)	36 (12.3)	49 (12.5)	0.956
	Sore throat	80 (11.7)	25 (8.6)	55 (14.0)	**0.029**
	Vomiting	75 (10.9)	25 (8.6)	50 (12.7)	0.085
	Weakness/Myalgia	67 (9.8)	6 (2.1)	61 (15.5)	**<0.001**
	Seizure	54 (7.9)	34 (11.6)	20 (5.1)	**0.002**
	Diarrhea	30 (4.4)	8 (2.7)	22 (5.6)	0.071
	Headache	16 (2.3)	4 (1.4)	12 (3.1)	0.163
	Mental status changes	5 (0.7)	2 (0.7)	3 (0.8)	1.000
Respiratory Finding	Wheezing	106 (15.5)	75 (25.7)	31 (7.9)	**<0.001**
	Dyspnea	49 (7.1)	31 (10.7)	18 (4.6)	**0.002**
	Ral and/or Ronkus	108 (15.7)	78 (26.7)	30 (7.7)	**<0.001**
	Prolonged expiratory phase	21 (3.0)	8 (2.7)	13 (3.3)	0.670
	Tachypnea	5 (0.7)	0 (0.0)	5 (1.3)	0.075
Underlying Disease	Prematurity	9 (1.3)	5 (1.7)	4 (1.0)	0.505
	Congenital heart disease	11 (1.6)	6 (2.1)	5 (1.3)	0.542
	Neuromotor retardation	11 (1.6)	6 (2.1)	5 (1.3)	0.541
	Diabetes Mellitus	4 (0.6)	3 (1.0)	1 (0.3)	0.317
	Bronchopulmonary dysplasia	3 (0.4)	2 (0.7)	1 (0.3)	0.578
Co-infection	Adenovirus	24 (3.5)	3 (1.0)	21 (5.3)	**0.002**
	RSV†	25 (3.6)	4 (1.4)	21 (5.3)	**0.007**
	SARS-CoV-2‡	7 (1.0)	5 (1.7)	2 (0.5)	0.120
Hospitalization	No	585 (85.2)	128 (43.8)	134 (34.0)	**0.009**
	Yes	101 (14.7)	164 (56.2)	260 (66.0)	
Oseltamivir Treatment	No	310 (45.2)	103 (35.3)	207 (52.5)	**<0.001**
	Yes	376 (54.8)	189 (64.7)	187 (47.5)	
Respiratory Support	Room air	576 (84.0)	238 (81.5)	338 (85.8)	0.129
	Oxygen support	103 (15.0)	50 (17.1)	53 (13.5)	0.192
	NIV§	6 (0.8)	4 (1.4)	2 (0.5)	0.213
	MV‖	1 (0.1)	0 (0.0)	1 (0.3)	0.349
Laboratory Values	Leukocyte (10^3/uL)	9.5±4.3	9.7±4.2	9.1±4.4	0.259*
	Neutrophil (10^3/uL)	4.4 (2.8-6.9)	4.4 (3.0-7.0)	4.3 (2.6-6.7)	0.418**
	Lymphocyte (10^3/uL)	2.7 (1.5-4.6)	2.7 (1.5-4.5)	2.6 (1.5-4.8)	0.959**
	Platelet (10^3/uL)	293±126	296±118	289±135	0.364*
	Albumin (g/L)	44±4.1	44.7±3.5	43.5±4.3	**<0.001***
	Procalcitonin (ug/L)	4.4 (4.1-4.82)	3.9 (0.11-4.8)	4.4 (4.1-4.9)	0.214**
	CRP†† (mg/L)	9.2 (3.5-10.8)	6.4 (1.7-19.1)	9.5 (9-10.1)	**0.001****
	Fibrinogen (g/L)	2.85±1.36	1.75±0.82	3.49±1.19	**<0.001***

All laboratory values are presented as mean ± standard deviation or median (25^{th}–75^{th} percentile).
¶Chi-square test, *Student's t-test, **Mann–Whitney U test
†RSV: respiratory syncytial virus; ‡SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; §NIV: non-invasive mechanical ventilation; ‖MV: invasive mechanical ventilation; ††CRP: C-reactive protein

median age was 42 (15–94) months among those with mild disease and 24 (7–64) months among those with moderate to severe disease, indicating a statistically significant difference ($p<0.001$). The comparison of mild and moderate-to-severe cases is detailed in Table 2.

Figure 2 illustrates vaccine recommendations and the proportion of vaccinated patients. In Group 1, compliance with vaccine recommendations from family physicians and pediatricians was 33% and 58%, respectively. In Group 2, the rates decreased to 31.5% and 43.7%, respectively. Notably, none of the vaccinated patients experienced moderate to severe disease, with all vaccinated patients falling into the mild disease category. However, data on the timing of influenza vaccination and the duration until admission were unavailable.

Table 2. Comparison of mild-to-moderate-severe disease

		Mild Disease n (%)	Moderate-Severe Disease n (%)	p[¶]
Sex	**Boy**	331 (55.6)	48 (52.7)	0.606
	Girl	264 (44.4)	43 (47.3)	
Influenza A		467 (78.5)	79 (87.8)	0.040
Influenza B		159 (26.7)	21 (23.3)	0.493
Group 1 (n=292)		267 (91.4)	25 (8.5)	**<0.001**
Group 2 (n=394)		314 (79.7)	80 (20.3)	**<0.001**
Underlying Disease	Prematurity	2 (0.3)	7 (7.9)	**<0.001**
	Congenital heart disease	5 (0.8)	6 (6.6)	**<0.001**
	Neuromotor retardation	7 (1.2)	4 (4.4)	0.024
	Diabetes Mellitus	3 (0.5)	1 (1.1)	0.483
	Bronchopulmonary dysplasia	1 (0.2)	2 (2.2)	**0.009**
Co-infection	Adenovirus	9 (1.5)	15 (16.5)	**<0.001**
	RSV[†]	11 (1.8)	14 (15.4)	**<0.001**
	SARS-CoV-2[‡]	1 (0.2)	6 (6.6)	**<0.001**

[¶]Chi-square test
[†]RSV: respiratory syncytial virus; [‡]SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

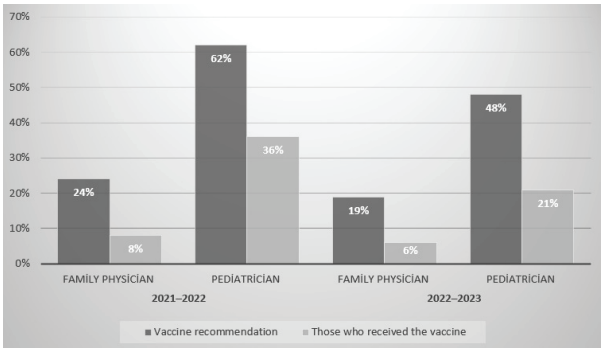

Figure 2: Vaccine recommendations for patients and families.

DISCUSSION

The primary finding of our study was that, following the relaxation of isolation measures, influenza severity increased, whereas the proportion of other viral infections, such as Adenovirus and RSV, increased. Furthermore, a decrease in physicians' recommendations for vaccination and diminished compliance among families were noted in the aftermath of the COVID-19 pandemic.

A notable increase in the mean age of patients diagnosed with influenza was observed in Group 2. The overall mean age was consistent with the findings of a comprehensive 20-year study (8). The observed age-group difference in Group 2 might be attributed to heightened transmission associated with the reopening of schools. Additionally, previous studies have indicated that the average age is higher among patients diagnosed with influenza B than among those diagnosed with influenza A (8). Thus, age differences may have occurred in Group 2, where the incidence of influenza B was higher.

Our study revealed a noteworthy shift in the timing of the influenza peak, which occurred 3 months earlier, accompanied by an overall increase in patient numbers throughout the year following the removal of isolation measures. This deviation from the previous year is attributed to school closures, mask use, adherence to hand hygiene, and reduced time spent in enclosed and crowded environments in the previous year. The abrupt decline in patient numbers from February onward, subsequent to the peak in the year when isolation measures were lifted, can be ascribed to the earthquake that affected a substantial part of the country on February 6, 2023. During this period, a hospital ward was reserved for earthquake victims, reducing hospital admissions. In addition, schools were closed for a month during this period. While a 20-year study indicated that influenza A typically constituted 80% of cases, with influenza B predominating in 5 out of 20 years (8), our study found influenza A to be predominant in both years, with an increase in influenza B cases in the year when isolation

measures were lifted. Furthermore, influenza A exhibits peak transmission 24–48 hours post-illness, whereas influenza B features two peaks, one before and one after illness (9). Hence, in the year when isolation measures were lifted, the surge in patient numbers and the earlier peak may be attributed to these factors.

Consistent with other studies, the prevalent symptoms in our study included fever, cough, and nasal discharge (10, 11). Seizures were observed in 7.9% of patients, a finding similar to that of a 5-year study with a large patient cohort (12). The higher seizure rate in Group 1 may be associated with delayed hospital presentations due to the curfew that year. Additionally, a previous study suggested a close relationship between influenza A and seizure frequency (8). Myalgia was more frequently observed in Group 2, and we suggest that this discrepancy may have arisen from the higher propensity of influenza B to induce myalgia, as evidenced by previous studies (13), coupled with a higher incidence of influenza B cases within Group 2. The higher frequency of respiratory symptoms in Group 1 may be attributed to influenza A predominance (14).

Post-isolation measures, RSV, and adenovirus incidence exhibited a statistically significant increase compared to the previous year. Our data appear to align with a previous study reporting a reduction in viral infections during the COVID-19 pandemic (15). A study published in the United States at the end of 2023, a rise in the prevalence of other viral agents was documented (16). Although not statistically significant, the incidence of scabies, also transmitted by contact, increased in the year isolation measures. This underscores the broader role of preventive measures, such as hand hygiene and mask use, in preventing the spread of various viral infections through close contact, which extend beyond the confines of the COVID-19 outbreak.

In the year following the removal of isolation measures, the number of moderate-to-severe cases was higher, as evidenced by elevated acute-phase reactants, such as C-reactive protein and fibrinogen, increased hospitalization rates, increased oseltamivir initiation rates, and longer durations of hospitalization and clinical recovery. Nearly half of the hospitalized patients in this study had no underlying cause (17). The co-infection rate in the group with a more severe disease course was significantly higher than that in the other group, potentially contributing to disease severity. The severity of the disease may progress more markedly in the presence of co-infections with other viral agents (18, 19). Additionally, during the COVID-19 pandemic, outpatient follow-ups were necessary for some patients due to hospitalization constraints. Consequently, physicians may have opted for broader indications for hospitalization in the following year. This may explain the prolonged duration of hospitalization in these patients. A previous study showed that patients admitted with influenza B infection had longer hospitalization durations than those with influenza A (8). The higher rate of influenza B in Group 2 may have also contributed to the longer hospital stay. Symptoms may be less severe in children who develop influenza despite influenza vaccination (11). Thus, the disparity in vaccination rates between the groups may also have contributed to the differing disease severity. The prevalence of underlying disease and co-infection was significantly higher in the group with more severe disease. Underlying diseases, including co-infections, may exacerbate the severity of influenza (20). Consequently, children with a history of premature birth, congenital heart disease, and lung diseases, such as bronchopulmonary dysplasia, should be approached with heightened caution.

The American Academy of Pediatrics and the Centers for Disease Control and Prevention advocate for the use of oseltamivir as a treatment for influenza in children (1, 20). Studies have shown that oseltamivir is associated with a reduction in the duration of illness by more than 1 day (4, 21). Owing to the retrospective nature of our study, an assessment of the duration of illness in patients starting oseltamivir treatment was unfeasible because the exact date of symptom onset and treatment initiation could not be determined. The increased frequency of oseltamivir use in Group 2 may be attributed to the higher incidence of moderate-to-severe disease in this group and evolving medical practices. Larger-scale prospective studies are warranted to comprehensively explore this topic.

Our study revealed a decline in the rate of vaccination recommendations by family physicians and pediatricians post-pandemic, accompanied by a reduction in the adherence rate among families. The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and the American Academy of Pediatrics advocate for universal annual influenza vaccination among individuals aged ≥6 months (3, 5). It is recommended that vaccination be administered before the onset of influenza activity in the community (3, 5). Considering that the post-pandemic influenza peak in our study occurred 3 months earlier than in the previous year, some families may have declined vaccination on the grounds that their children had already acquired influenza. Nevertheless, evidence suggests that both influenza A and influenza B can co-circulate in the same year (8). Therefore, increasing vaccine recommendation rates has the potential to mitigate the impact of influenza epidemics.

Our data closely align with the Weekly Influenza Surveillance data published by the Ministry of Health, suggesting that they accurately depict the influenza trends in Turkey (22, 23).

Limitations

Our study has several limitations. The retrospective, single-center design introduces inherent biases and limits the generalizability of the findings. Crucial information, such as the incidence of acute otitis media, the most prevalent complication of influenza, and the date of initiation of oseltamivir treatment, remains undisclosed due to data unavailability. Furthermore, the reasons underlying families' decisions to abstain from vaccination were not elucidated, representing a significant data gap. Although general isolation precautions were observed, the study's efficacy may have

been compromised due to insufficient clarification regarding individual hand hygiene practices and adherence to isolation protocols. Additionally, the absence of the pre-pandemic period in the study design could have affected the statistical power. Fluctuations in the periodicity and annual impact of influenza outbreaks may have also diminished the accuracy of the study; however, given that our study was cross-sectional in nature, establishing a causal relationship was not feasible. Another constraint concerns the inability to distinguish between the subtypes of influenza A, which could have provided nuanced insights into its epidemiological dynamics. These limitations underscore the need for cautious interpretation of our findings and highlight avenues for improvement.

CONCLUSIONS

The prevention of viral outbreaks can be effectively achieved through the adoption of simple yet impactful measures, including meticulous hand hygiene practices and the consistent use of face masks. Mitigating disease burden and alleviating disease severity necessitates concerted efforts to enhance vaccination rates. This can be accomplished by encouraging increased vaccination recommendations from family physicians and pediatricians. Moreover, the implementation of vaccination programs, supported by government initiatives, plays a pivotal role in achieving widespread immunization coverage, thereby contributing to the overall reduction of disease prevalence and severity within the population.

Ethics Committee Approval: This study was approved by the ethics committee of the Clinical Research Ethics Committee of the Health Sciences University, Haseki Training and Research Hospital, decision number 62/2023.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- B.O., C.U., C.T.A., K.Ş., G.A., Z.Ü.O.; Data Acquisition- F.A., O.H., E.Ö., N.A., A.A..; Data Analysis/Interpretation- B.O., C.U., G.A.; Drafting Manuscript- B.O., G.A., F.A., O..H, E.Ö., N.A.; Critical Revision of Manuscript- B.O., C.U., C.T.A., K.Ş., Z.Ü.O,.A.A.; Final Approval and Accountability- B.O., C.U., K.Ş., G.A., F.A., O.H., E.Ö., N.A., C.T.A., Z.Ü.O., A.A.

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