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Original Article

Immunization Practices and Adverse Events Following Vaccination in Infants Admitted to The Neonatal Intensive Care Unit

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Abstract

Objective: To determine if vaccinations administered in the neonatal intensive care unit (NICU) were administered following Centers for Disease Control and Prevention guidelines while assessing for adverse reactions in the 48 hours post-vaccination.

Study Design: Retrospective cohort study of infants who received Diphtheria-Tetanus-Pertussis, inactivated Polio, Hepatitis B vaccines during NICU admission from February 2016 to January 2017 with a total of 337 immunization events reviewed. Data were assessed to determine vaccination delay according to recommended schedules as well as rate of adverse events. Knowledge base and attitudes were evaluated through a questionnaire administered over a three-week period to NICU care providers.

Results: Of the 337 immunization events reviewed, 256 vaccines were administered within 7 days of the recommended vaccination schedule, leaving 24% (n=81) administered outside of this schedule. Taking into account weaning of respiratory support and deterioration of respiratory status in the 48 hours prior to vaccination, total adverse event rates for the remaining 312 immunization events were 2% (n=7). Questionnaire showed many providers felt adverse events are commonplace following vaccination and highlighted a possible gap in knowledge of recommended vaccination guidelines.

Conclusions: This study suggests neonates admitted to the NICU are at risk for vaccination delay. Immunizations have a low rate of adverse events, thus confirming safety. Factors that may increase adverse events post-immunization include coincidental worsening of overall status and recent wean in respiratory support. Further studies are needed to examine best practices to promote improved vaccination in the NICU.

Keywords: prematurity; vaccine; NICU; preterm; immunize

Introduction

Immunizations outside of the newborn period are routinely administered to infants in the neonatal intensive care unit (NICU) given the length of stay of these high-risk neonates [1,2]. This practice is of critical importance, as this population is at risk for re-hospitalization from vaccine-preventable illnesses. Vaccination is regarded to be safe for premature infants to receive in the NICU [3,4]. There is a paucity of data regarding vaccination practices in NICUs; however, the current literature demonstrates that there is variability in how neonatologists comply with the recommended vaccination schedule from the Centers for Disease Control and Prevention (CDC), impacting the immunization rates of infants in the NICU. In the United States, very-low-birth-weight (VLBW; <1500 grams at birth) neonates are at risk for immunization delays as compared to normal birth weight neonates [1,5,6]. At age 12 months, VLBW infants are less likely to be up-to-date for all immunizations (odds ratio = 0.556; P=0.001) [7]. Additionally, a significant proportion of all infants discharged from the NICU on or after 2 months of age is under-immunized at the time of discharge [1,5,8]. In California, a 2012 review of 6 NICUs demonstrated that 51% of infants discharged from the NICU were up-to-date for routine immunizations [1]. Internationally, there is variable adherence to immunization guidelines in neonates born VLBW [3,9]. In Peru, vaccination rates of 35% are reported at age 7 months in VLBW infants [10]. This has contributed to a significant proportion of infants discharged from the NICU being under-immunized [1,2]. Delays in immunizations place infants at risk for vaccine-preventable diseases. Under-vaccination with Diphtheria-Tetanus-Pertussis (Dtap) vaccine increases the risk of pertussis among neonates 3-36 months of age [11]. A delay in vaccination by as few as 16 days is associated with increased rates of pertussis infections in infants under the age of 1 year [12,13]. Preterm infants demonstrate higher rates of pertussis-related hospitalization compared to full term infants [14]. Rates of hospitalization for infants with 1 dose of a pertussis vaccine prior to onset of disease are lower than for unvaccinated infants of the same age [15].

There have been conflicting studies reporting on adverse events following vaccination in the NICU. Vaccination in clinically stable preterm infants is generally regarded to be a safe medical procedure. Internationally, it is reported that vaccinations do not have major adverse effects in these infants [4,6,16,17]. There are also reports of increased apnea and bradycardia,

primarily in infants with chronic illness when administering Dtap-inactivated Polio vaccine (IPV)- Haemophilus influenzae type B (Hib)-Hepatitis B vaccine (HBV) or Dtap-IPV-Hib immunization [18,19]. In these studies, the apnea and bradycardia events were more common in infants with ongoing respiratory support, and those with a lower corrected gestational age. Additional reports indicate an increased incidence of sepsis evaluation and increased respiratory support with routine immunization in the NICU [20]. In other studies, when comparing the occurrence of adverse events between infants less than 29 weeks gestational age and above 29 weeks gestation age, there were no statistically significant differences in the rate of adverse events following vaccination [4]. It is also documented that immunizations in preterm infants are not associated with cardiac electrical activity variations [18]. Reviews of immunization in the NICU internationally demonstrate that they are well tolerated and safe [21]. However, some international studies report increased apnea and/or bradycardia within 48 hours following vaccination in preterm infants [22,23]. These findings highlight the conflicting reports of adverse event rates following vaccination in the NICU. Furthermore, some reports call for cardiorespiratory monitoring following vaccination in the NICU; however, there are currently no universal recommendations regarding this [19,24]. Nonetheless, it is recommended that vaccination take place on time in the NICU rather than delay vaccination [4,18,25,26].

Aim of Study

Given the paucity of data regarding vaccination practices in NICUs, the risk of vaccination delay reported in high-risk neonates, and the conflicting findings of adverse outcomes noted in the research, we sought to determine whether vaccinations administered in a large, level IV NICU were administered in accordance to CDC guidelines, the knowledge and perceptions care providers had regarding vaccinations, and for those infants who received vaccination in the NICU, to assess if adverse reactions occurred in the 48 hours following vaccination.

Methods

This study was a retrospective cohort study of preterm infants admitted to the NICU at Children's Memorial Herman Hospital between February 2016 and January 2017. This review was conducted as part of ongoing quality improvement initiative surrounding vaccine practices in the NICU, and met the criteria defining a quality improvement project per the University of Texas Health Science Center at Houston McGovern Medical School Committee

for Protection of Human Subjects as well as Institutional Review Board (IRB) exemption from Memorial Hermann Hospital system (IRB number HSC-MS-19-0834). Patients were identified by searching for infants who had received the Dtap-IPV-HBV vaccination using the billing code for the vaccination. Once patients were identified, their medical record was reviewed to determine the date of vaccination, which vaccinations were given, and whether vaccinations were given within 7 days of the recommended CDC vaccination time (i.e. 60 days of life, 120 days of life, etc.). In addition to the timing of the vaccination, the medical record was reviewed to determine whether there was a deterioration in medical status following vaccination, specifically respiratory status, fever, and feeding intolerance. Infants excluded from review were those who did not receive or have documentation of receiving the Dtap-IPV-HBV vaccine while admitted to the NICU. The patient population ranged in chronological age from 55 days of life to 366 days of life. Gestational age at birth ranged from 23 0/7 weeks to term, as demonstrated in Table 1.

The respiratory status of a patient was identified by evaluating the 3 days preceding vaccination in order to determine the baseline. A change in respiratory status was defined as an increase in respiratory support (i.e. a step up in support such as any increase in nasal canula flow, or any change from room air to nasal canula or high flow nasal canula; for infants on mechanical ventilation, increase in rate, pressure support, positive end-expiratory pressure, by more than 4 or an increase in apnea and bradycardia episodes in the 48 hours following vaccination. Whether respiratory support had been decreased in the 3 days prior to vaccination was also collected. Fever was defined as temperature of 100.0 F in the 48 hours after vaccination. Physicians' notes document fever as 100.1 F. Any sepsis evaluation, defined as obtaining blood cultures and starting empiric antibiotics within the 48 hours following vaccination was assessed. The patient was considered to have had sepsis if antibiotics were continued for longer than 48 hours. Sepsis was disproven based on cultures negative at 48 hours, infant clinically well, and antibiotics stopped. Feeding intolerance was defined as a change in feeding pattern from baseline in the 48 hours following vaccination reflected by an increase in documented feeding residuals and decreased ability to complete feeds orally by greater than 20% compared to baseline in the preceding 3 days.

Attitudes and knowledge base of neonatal providers toward vaccination was assessed

through voluntary participation in a brief, anonymous survey conducted over a period of 3 weeks. Neonatal physicians, fellows, nurse practitioners and bedside nurses working at Children's Memorial Hermann Hospital received email notifications of the survey as well as had access to study links posted in common work areas via QR codes. Qualtrics was utilized to create the survey and analyze the data.

Statistics

Statistical Package for the Social Sciences descriptive analysis and frequencies was used for the analysis of data.

Results

A total of 337 immunization events were administered between February 2016 and January 2017. Of those vaccines, 320 were Dtap-IPV-HBV/Hib/Pneumococcal conjugate vaccine (PCV13) (given as three separate injections on the same day), 8 were the inactivated intramuscular influenza vaccine, 8 hepatitis B monovalent, and 1 hepatitis A vaccine. Immunizations given at the same time were grouped as one immunization event. Of those administered, 256 (76%) fell within 7 days of the CDC recommended schedule. A total of 81 (24%) vaccines were administered late. Of the immunization events that were administered late, 57% were administered more than 14 days late. The delay in vaccination ranged from 8 days to 6 months. Table 2 indicates the documented reasons for delaying vaccination. For those infants who experienced vaccination delay, 48 (59%) had no documentation in the medical record explaining the delay. "Medically unstable infant" was the primary documented reason for vaccine delay, occurring in 17 infants (21%).

Worsening Respiratory Status. Charts were reviewed to determine if there was a change in clinical status within the 48 hours following vaccination. Table 3 summarizes the findings. Of the 337 immunization events reviewed, there were 32 (9%) infants who required a change in respiratory support following vaccination, defined as having an increase in respiratory support. Increases in support included increasing flow via nasal cannula, or increasing the amount of continuous positive airway pressure (CPAP). No infant required intubation and no infant required increased ventilator settings. Of the 32 infants who experienced an increase in their respiratory support, 17 (53%) had undergone a wean in respiratory support within 48 hours of vaccination. An additional 8 infants had worsening respiratory status within the 48 hours prior to vaccination (25%) as indicated by increasing respiratory support or increased episodes of apnea and/or bradycardia.

One infant developed a mucus plug while ventilated on the evening following vaccination, and returned to baseline shortly after it was resolved. One infant developed upper respiratory infection symptoms and subsequent desaturations requiring nasal cannula the day following vaccination, and had a family member visit with similar symptoms just prior to vaccination. The gestational age of the infants in this group ranged from 23 weeks to 40 3/7 weeks, with 53% of the infants being between 23 0/7 weeks and 24 6/7 weeks. Overall, of the 32 infants experiencing a change in respiratory support, 27 infants (84%) had status changes within 48 hours preceding the vaccination, which could explain their need for respiratory support, independent of vaccination delivery. Of the 337 vaccination events, only 5 (1.5%) experienced a need for increased respiratory support within the 48 hours following vaccination without other factors noted in the 3 days preceding vaccination.

Apnea/Bradycardia. Twenty-eight infants had increased apnea and/or bradycardia events within 48 hours following vaccination. Of those 28 infants, 12 (43%) had undergone a wean in respiratory support within 48 hours preceding vaccination. Additionally, 8 more infants (29%) had worsening respiratory status in the 48 hours prior to vaccination. Thus, 20 (71%) of the 28 infants with increased apnea/bradycardia events following vaccination were noted to have had a decrease in respiratory support or an increase in events prior to vaccine administration. Seven infants (2%) experienced increased apnea/bradycardia following vaccinations without increases in respiratory support or worsening overall status prior to vaccinations.

Fever and Sepsis. Seven infants (2%) experienced fever within 48 hours after vaccination. The temperature range was from 100° F- 101°F. Of those infants, 1 underwent a sepsis evaluation, which was ultimately negative.

A total of 4 infants (1%) underwent a sepsis evaluation in the 48 hours following vaccination. Of the 4 infants, 1 underwent a sepsis evaluation for fever and worsening respiratory status, 2 underwent evaluation for worsening respiratory status, and 1 infant underwent evaluation due to feeding intolerance. In all infants, antibiotics were discontinued after 48 hours as sepsis was not proven.

Feeding Intolerance. Four infants (1%) experienced feeding intolerance in the 48 hours following vaccination. Two infants had a decrease in their oral intake (where prior was finishing all feeds orally, to only partially completing feeds and requiring gavage

feedings); 1 infant was changed to NPO status, and 1 infant had a single feed held overnight, and resumed normal feeding in the following morning. All infants returned to baseline feeding habits within 48 hours following vaccination.

Attitudes of NICU Providers. A total of 26 participants responded using the survey with a population of the following: 7 attendings, 3 fellows, 9 neonatal nurse practitioners (NNP), 5 neonatal nurses, and 2 discharge planners. Table 4 shows the barriers to discharge as reported by the NICU cohort. The group as a whole recognized the importance of vaccination, 100% strongly agreed, and acknowledge their role as an essential part in preventing disease, 96.15% strongly agree while 3.85% somewhat agrees. Opinion was divided though when it came to who was responsible for consenting and ordering vaccines on the appropriate schedule. Most participants agreed it was the responsibility of the bedside nurse to obtain consent for vaccination with 11.5% reporting that they neither agreed/disagreed or disagreed. Even so, when that same responsibility was suggested for placement on the physician or NNP, the physicians, fellows, nurse practitioners, and discharge planners felt like it was not their responsibility. This was in opposition to bedside nurses who agreed the role should fall on the physician or NNP, 80% of nurses agreed with this statement. Attendings, fellows, NNP, and discharge planners mostly agreed that it is the responsibility of the bedside nurse to ask for vaccination orders. Again, this went against the nurses with whom 80% disagreed. The entire cohort felt in agreement that the physician or NNP are responsible for ordering vaccines on time. With reference to adverse events following vaccination in the NICU, two attendings neither agree nor disagree, 1 fellow somewhat disagreed, and a discharge planner somewhat agreed that they are worried vaccines will cause a setback for a neonate. The rest of the cohort strongly disagreed with the previous statement.

Knowledge Base of NICU Providers. Table 5 includes the quiz questions and results collected assessing the knowledge base of NICU providers over vaccination. Table 6 lists the results of providers by group on the assessment. Overall fellows in neonatology had the highest quiz score of 93%, while attendings and NNP averaged a 71% and 78% respectively. Neonatal nurses and discharge planners had the lowest knowledge base with an average score of 37% each.

Discussion

Vaccinations are recommended to protect infants from various communicable diseases.

However; preterm infants often spend months in the NICU, and for a variety of reasons may not be vaccinated on time [1]. Though the majority of infants in our NICU were vaccinated on time, we have found a 24% rate of vaccination delay in the NICU, with only 1-2% of included infants experiencing worsening clinical status that could not be explained by factors outside of recent vaccination. Additionally, documentation for delay in vaccination was often lacking, leaving the reasons behind delays in vaccination unclear. Using data gathered from the questionnaire, NICU care providers seem to suggest a difficulty getting consent from parents, 40% of responses, as a primary reason. The possibility of an adverse event or recent illness, approximately 33% of responses, are also documented as reasons for delaying vaccination schedule.

In the United States in 2014, only 71.6% of infants aged 19-36 months were up-to-date with recommended combined 7 vaccine series [27]. Though there is limited data regarding rates of vaccination in NICUs, our findings are consistent with previous studies in this population. Navar-Boggan et al (2012) [1] reported under-immunization at the time of discharge from the NICU, noting that only 51% of infants were up-to-date for routine vaccination at the time of discharge. Langkamp et al (2001) [7] revealed that in the United States, VLBW neonates were significantly less likely to be up-to-date for all immunizations at age 12 months. In Australia, Crawford et al (2009) [3] surveyed neonatologists regarding their adherence with immunization guidelines and discovered highly variable vaccination practices which contributed to preterm infants experiencing delayed vaccination. Under-vaccination increases the risk of vaccine-preventable disease, and vulnerable populations like preterm infants are at increased risk of hospitalization due to vaccine-preventable illnesses including pertussis [11,14]. Thus, it is imperative to protect infants from vaccine-preventable disease whenever possible.

We found that 53% of neonates with delayed vaccination lacked explanatory documentation in the medical record demonstrating that vaccination in the NICU is an area for continued quality improvement in neonatal care. Though not often documented, concern for worsening clinical status following vaccination serves as an anecdotal explanation for vaccination delay. Our data demonstrates a rate of adverse events post-vaccination to be less than 9.5%. Interestingly, it was noted that increased respiratory events tended to coincide with recent respiratory status changes prior to vaccination, either recent weaning of respiratory support or

overall worsening status. Of the infants who experienced a respiratory support increase following vaccination, 53% had a wean in support just prior to vaccinations, and thus it is not known if the vaccines caused the increase in support, or if the infant failed weaning for other reasons. When removing these patients, this revealed an adverse event rate of 2%. Additionally, it was uncommon to observe fever or feeding intolerance in preterm infants post-vaccination. No infant demonstrated a need for intubation post-vaccination, and no infant developed confirmed sepsis. However, at least 30% of the provider responses indicate the possibility of an adverse event as a barrier to vaccination. This along with some concerns expressed by physicians who are worried vaccines will cause a setback for neonates suggest attitudes may have a role in administering vaccines on time. Previous studies have revealed mixed results in the rate of adverse events post vaccination in the NICU. Lee et al (2006)]19] reported an increase in adverse cardiopulmonary events following the first dose of Dtap-IPV-Hib in preterm infants, and that most of these events were of limited clinical significance. In 2007, Pourcyrous et al [28] revealed that 16% of their infants had vaccine-associated cardiorespiratory events within 48 hours post-immunization. Similar findings were discovered by Faldella et al [18] in 2007, with an 11% rate of apnea/bradycardia/desaturation related to vaccine administration. McCrossan et al (2015) [4] reported that, within the NICU setting, there were no reported adverse events in their population who had received the first set of vaccinations (Dtap-Hib-IPV, Hib, PCV HBV). In 2016, Wilinska et al]24] found that vaccination of clinically stable preterm infants at term age is a safe medical procedure, noting rates of apnea following vaccination at 4%. In that population, it was noted that long-term respiratory support and late infections were risk factors for apnea following vaccination. Currently, there is no formal recommendation to monitor neonates post-vaccination. Our study correlates with recent studies demonstrating the safety of vaccination in the NICU. However, previous studies failed to account for respiratory support changes made just prior to vaccination. It is not possible to know if the respiratory wean failed or if the vaccines impacted the success of the respiratory wean. Providers should consider temporally spacing out intentional changes to respiratory status and vaccination administration in order to decrease potential changes in respiratory status post-vaccination.

In evaluation of attitudes around vaccination, there was disagreement between nursing staff

and physician or NNP as to who was primarily responsible for obtaining consent and orders for vaccination. This disconnect could contribute to vaccination delay, and thus highlighting the need for a consensus in the NICU that engages all levels of providers. Neonatal fellows had the strongest scores on the knowledge-based assessment, which may be attributed to recently completing a general pediatric residency training program. Nurses and neonatal discharge planners were least knowledgeable. This again highlights the need for a systems-based approach to sharing knowledge and policies on vaccination.

The overall aim of our study was to examine if infants in the NICU received vaccinations according to CDC recommendations. This study is limited in that it does not include infants who were not vaccinated in the NICU due to other reasons, including parental refusal. This could lower the overall vaccination rate within this NICU. There was limited documentation in the medical record to explain vaccination delays as well. While providers were surveyed to better assess their current practices, these attitudes are limited by the amount of responses as well as gaps in knowledge observed through the assessment of a quiz at the end of the questionnaire.

Conclusions

In conclusion, we have demonstrated in a large, level IV NICU with high acuity that the rate of adverse events following vaccination is low, though delay in vaccination still occurs. Providers in the NICU should aim to vaccinate infants on schedule when possible so as to avoid infants experiencing delay and thus susceptibility to vaccine-preventable illness. If an infant is ready for a decrease in respiratory support at the same time that child is due for vaccination, providers may consider vaccinating the infant and observing their overall status prior to decreasing the ventilator support. We argue that due to confusion on who is responsible for consent and ordering of vaccinations, all team members should have awareness of vaccination, and that NICU administration should establish protocols and leaders to increase awareness among all levels of providers.

Future studies are needed to determine methods to improve vaccination in the NICU, including the use of electronic medical records to prompt providers on vaccination status. Clear roles and responsibilities with respect to consenting, and ordering vaccines may improve overall vaccination rates, as well as providing education on vaccine schedules. Engaging parents, neonatal nurses, NNP and neonatologists will be

needed to implement techniques to improve vaccination rates in the NICU.

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Table 1: Demographic and Respiratory Characteristics

Characteristic	
Demographic and perinatal characteristics	
Birth weight (g)…mean (SD)	1203(807)
Median birth weight (g)	840
Gestational age (wk)…mean (SD)	28 (4.89)
Median gestational age (wk)	26
Corrected gest. age (wk) at vaccinationmean (SD)	41 (7.8)
Median corrected gestational age (wk) at vaccination	40
Multiple gestation (%)	10
Race/ethnicity (%)	
Non-Hispanic black	33
Non-Hispanic white	23
Hispanic	26
Asian	4.5
Other	14
Male	52
Respiratory characteristics at time of vaccination (%)	
Intubated	21.4
CPAP	17
High-flow nasal cannula	8.6
Nasal Cannula	13
Room Air	40

g: grams; SD: standard deviation; wk: weeks; CPAP: Continuous positive airway pressure

Table 2: Reasons documented for vaccination delay

Item	**N (%)**
No documentation	48 (59.26)
Awaiting signed consent	10 (12.35)
Medically unstable	17 (20.99)
Vaccination not available (shortage)	2 (2.47)
Parental request to delay	1 (1.24)
Delayed to stay on track with sibling	3 (3.7)
Total	**81**

Table 3: Adverse events following vaccination (Total study n=337)

Item	N (%)
Infants with change in respiratory support*	32 (9.94)
Recent wean in support	17 (53.13)
Recent worsening status	8 (25)
Overnight ventilator mucus plug (resolved after treatment)	1 (3.12)
Visiting parent with URI	1 (3.21)
Infants with change in respiratory support without confounding factors*	5 (1.48)
Infants with increased A/Bs*	28 (8.31)
Recent wean in support	12 (42.86)
Increasing A/Bs prior to immunization	8 (28.57)
Visiting parent with URI	1 (3.57)
Infants with increased A/Bs without confounding factors*	7 (2.08)
Infants with axillary temperature >99.9F*	7 (20.8)
Infants undergoing sepsis evaluation	1 (14.29)
Infants undergoing sepsis evaluation*	4 (1.19)
Infants with proven sepsis*	0 (0)
Infants with feeding intolerance*	4 (1.19)
Infants with poor nippling	2 (50)
Infants with increased residuals	2 (50)

URI: upper respiratory infection; A/Bs: Apnea/Bradycardia *= as compared to total vaccination events for study (n=337)

Table 4: Reported barriers to vaccination

Barriers	**%**
Unable to get consent	39.1%
Infant too sick at the time they are due	25.0%
No reminder system	10.9%
Want to wait so baby will not get sick	7.8%
Following a delayed schedule per another provider's plan	6.3%
Other - Parental hesitancy - Nurse forgot to consent - Infant previously critical, if infant deteriorate may be from vaccine - Live vaccines have to wait for discharge	6.3%
Forgetting to order	4.7%

Table 5: Vaccine knowledge assessment (n=26)

Questions with answers	**% correct**
For a newborn weighing 2kg or more, the hepatitis B vaccine is recommended: within 24 hours of birth	84%
For a newborn weighing less than 2 kg, the hepatitis B vaccine is recommended: at one month of life	80.8%
The earliest the Dtap, Hib, PCV, or IPV vaccines can be given is: at 6 weeks	11.5%
Which vaccines are recommended at 2 months: Dtap-PCV-Hib-IPV	92.3%
If an infant received vaccines late, what is the minimum interval between dose 1 and dose 2 for Dtap: 4 weeks	64.0%

kg: kilograms; Dtap: Diphtheria-Tetanus-Pertussis; Hib: Haemophilus influenzae type b; PCV: Pneumococcal vaccine; IPV: Inactivated Polio Vaccine

Table 6: Provider score on vaccine knowledge assessment

Provider Role	Average Score	Percentage
-Attending	3.57/5	71.4
-Fellow	4.67/5	93.3
-Neonatal Nurse Practitioner	3.89/5	77.8
-Neonatal Nurse	1.85/5	37.0
-Discharge Planner	1.87/5	37.5

Citation: McKay, S., Sargent, C., Domonoske, C., McKay, K., Duncan, A. Immunization Practices and Adverse Events Following Vaccination in Infants Admitted to The Neonatal Intensive Care Unit. Annals of Neonatology Journal, 2020; (): -. doi: 10.21608/anj.2020.27829.1010