Assessment of Neonatal Screening Program within Five years in Holy Karbala Governorate /2018

A Thesis
Submitted to the Council of College of Medicine – University of Kerbala as Partial Fulfillment for the degree of Higher Diploma in Family Medicine

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بسم الله الرحمن الرحيم

((يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ))

صدق الله العلي العظيم

[المجادلة: 11]

Certification of supervisor

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Dedication

This thesis is dedicated to my parents who have always loved me unconditionally and whose good examples have taught
me to work hard for the things that i aspire to achieve
The work is also dedicated to my lovely husband who gave me strength when I thought of giving up , who continually provide his moral ,spiritual and emotional support.
To my brothers and my sister who have always been a constant source of support and encouragement during the challenges of whole the study.
To my lovely son who have made me stronger and more fulfilled than I could have ever imagined .

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And lastly I’d like to thank all health care staff in screening program unite in Karbala teaching hospital for children who helps me in complete my study

This thesis is only a beginning of my journey

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List of Abbreviations

Abbreviations	Meaning
DBS	Dried blood spot
FP	Filter paper
K	Number of inhabitants (10000)
mg/Dl	Milligrams per deciliter
n phenylalanine	Neonatal phenylalanine
n total galactose	Neonatal total galactose
n TSH	Neonatal Thyroid stimulating hormone
NBS	newborn screening
nmol/ml	Nano moles Per milliliter
PHC	Primary health care centers
TSH	Thyroid stimulating hormone
U/g Hb	Unit Per gram of Hemoglobin
µU/Ml	Micro Units Per milliliter

Abstract

Background: Newborn screening is a comprehensive system that includes laboratory testing, diagnosis, follow-up, treatment, education, and evaluation. To be effective and successful, the newborn screening system requires continuous quality improvement focused on information sharing, technical assistance and standardized data. The screening program targeting infants in the first month of age for congenital hypothyroidism, phenylketonuria and classical galactosemia. Metabolic disorders are not easily detected without screening because many of the symptoms are nonspecific and look like other more common disorders. Some of the disorders do not show any symptoms at all until damage has been occurred. In some of these cases damage irreversible. Screening means that metabolic disorders can be diagnosed before a baby gets sick.

Objectives: to assess the neonatal screening program in Karbala governorate between 2013-2018 and to estimate the incidence of congenital hypothyroidism, phenylketonuria and galactosemia in Karbala and identify the obstacles or limitations in the program.

Methods: a biometeric study conducted among all newborn below than 1month underwent screening from the beginning of program at the first of April 2013 to 31 of March 2018 (5 years), study involve all 4 health sectors which belongs to Karbala Health Directorate. By reviewing of their records and screening results and further analyzing the data. Coverage rate, positive screening test percentage, incidence, positive predictive value and specific program indicators were measured.

Results: The total coverage rate was 71.7% and slightly improve between 2013 toward 2018. The incidence of congenital hypothyroidism was 1:1538 and male to female ratio was 1.1:1, the incidence of phenylketonuria was1: 7692 and incidence

of galactosemia was 1:934. Defaulters was identifying in different stage of program. The mean age at first sampling for those with positive screening test was11.4±7.8 days and median was 10 days, the mean age at second sampling was26.5 ±9.8 days and median was 23 days. The percentage of neonate that done the first sampling at age ten days and younger was generally low and under the international standard, the percentage of screening card samples to be received by the laboratory within 6 days of being taken was generally the same and above the international standard, the percentage of result to be available within four working days from date of received to lab and the percentage of neonates who diagnosed and received appropriate treatment by 28 days of age was increase between 2013 to 2018 but generally below the international standard. Regular follow up was 53.6% for congenital hypothyroidism, 91.6% for phenylketonuria and 25% for galactosemia.

Conclusions**:** generally, the program important and effective and need to be expanded to cover all Iraq. However, the coverage rate in Karbala Health Directorate was suboptimal compared to the international standard as well as the overall results of screening test, age of screening sampling, lab performance and follow up were below the international standard.

CHAPTER

ONE

INTRODUCTION

Definition of newborn screening:

Newborn screening (NBS) is a comprehensive system that includes laboratory testing, diagnosis, follow-up, treatment, education, and evaluation. To be effective and successful, the NBS system requires continuous quality improvement focused on information sharing, technical assistance and standardized data **((NewSTEPs) 2016)**.

Aim of (NBS) is to identify a particular rare, but hereditary, critical, metabolic either or both congenital disorders that possibly will be life threatening **(Alkhazrajy and Adnan 2016).** Screening is the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not **(Wilson, Jungner et al. 1968)**. Newborn screening in which each newborn infant is screened for up to50 specific metabolic disorders for early detection and intervention is the first program of population wide genetic testing. As a public health intervention, NBS has greatly improved the lives of thousands of affected children **(Green, Dolan et al. 2006)**

Choice of illness in the screening program should be built on the significances of the personal country. In this consider, the Wilson and Jungner criteria**(Wilson, Jungner et al. 1968)** can help as a beneficial model These were:

1) Clinically and biochemically well recognized disorder.
2) Identified incidence in populations
3) Disorder associated with significant morbidity and mortality.
4) Effective treatment available.
5) Period before which intervention improves outcome.
6) Availability of an ethical, safe, simple and robust screening test
7) Cost-effectiveness of screening.

Epidemiology of genetic disease:

Globally, at least 7.6 million children are born yearly with severe genetic or congenital malformations; 90% of these are born in mid and low income countries**(Kaur and Singh 2010)**.

In the Middle East and North Africa area (MENA), the population in the region is about 400 million, with high birth rate and an estimated 10 million newborns per year. The majority of the population is of the Islamic faith and mostly Arab. The population is characterized by a high consanguinity (25–70%) and a high percentage of first-cousin marriages **(Saadallah and Rashed 2007)**.

Haemoglobin disorders, inherited metabolic disorders, neurogenetic disorders and birth defects are relatively common among the population.**(Saadallah and Rashed 2007)**.

History of newborn screening :

The story of neonatal screening dates occur in 1959 when Dr Robert Guthrie established a test to discover extreme phenylalanine amounts by microbiological bacterial inhibition test on the dry blood spot (DBS) taster gathered on a filter paper(F.P) which also called with (Guthrie card) to confirm phenylketonuria in all neonates **(Guthrie and Susi 1963).**

Guthrie test turn out to be a routine in United States of America in 1962 **(Therrell and Adams 2007).** Newborn screening programs, introduced in the 1970 have improved the early diagnosis and treatment of several genetic diseases that are asymptomatic during the neonatal period. Their early detection can improve prognosis and lead to a newborn's full development**(Botler, Camacho et al. 2012).**

Dussault presented investigation for congenital hypothyroidism **(Dussault, Coulombe et al. 1975)**. Following the diffusion and inception of newborn screening for Phenylketonuria in the early sixties, classic galactosemia was firstly added to the panel Since then, numerous countries are screening for this disease, despite the criticisms about the opportunity of this procedure, treatment ineffectiveness on long-term outcome **(Porta, Pagliardini et al. 2015)**.

Neonatal Screening Program in Iraq:

Newborn screening program in Iraq has been begun on April, 2013 when a pilot project implemented that includes two governorate: Baghdad and Karbala. The initial stage for further than 1year has concentrating on ability building creating the best efficient technology for first detection of two assigned disorders of inborn error of metabolism such as, phenylketonuria, galactosemia also congenital hypothyroidism by (DELFIA technique), taken the blood from heel of baby by prick **(MOH 2014)**

To test for these diseases, blood Sample is collected at proper age (72 hours-5days) after birth and moreover up to 2 month of age those who had not investigated in hospitals that have neonate care units and primary health care centers(PHC). Screening is the 1st step in a 2-step procedure. The initial test specifies a problem might be existing (primitive) , to proves whether or not the problem or illness is existing ,a 2nd diagnostic test (confirmative) are done. The blood is dried onto a neonatal screening filter paper. This project will participate in reducing the rate of under-five mortality by two-thirds, to meeting Millennium Development Goal 4 between (1990-2015) **(MOH 2014).**

Disorders screened in Iraq:

1. Congenital hypothyroidism:

Congenital hypothyroidism is the most common cause of preventable mental retardation in children. Thus screening programs of Congenital hypothyroidism have been started for better management of the condition and preventing its related neurodevelopmental consequences **(Hashemipour, Hovsepian et al. 2018).** Congenital hypothyroidism is classified into transient and permanent Congenital hypothyroidism. A persistent deficiency of thyroid hormone leads to permanent Congenital hypothyroidism that requires life-long treatment.

A temporary deficiency of thyroid hormone lead to transient Congenital hypothyroidism discovered at birth, but then recovering to normal thyroid hormone production**(Rastogi and LaFranchi 2010).**

Normal thyroid function is necessary for the growing and neurodevelopment of newborns and young children. Anomalies of thyroid gland growth, function and immigration can all cause Congenital hypothyroidism **(Simpser and Rapaport 2010)**. When the thyroid gland fails to develop or function properly, Congenital hypothyroidism occurs. The thyroid gland is absent in 80 to 85 percentage of cases, severely reduced in size (hypo plastic), or abnormally located. These cases are classified as thyroid dysgenesis **(De Felice and Di Lauro 2004)**. Congenital hypothyroidism is caused by inborn errors in the molecular steps of thyroid hormones biosynthesis, secretion or recycling in the remaining 15-20% of cases, These forms of congenital hypothyroidism are specified with the term "dyshormonogenesis", and are characterized by an enlargement of the gland (goiter), probably due to elevated TSH levels **(Nettore, Cacace et al. 2013)**.

According to world-wide data taken from neonatal thyroid screening programs Congenital hypothyroidism occurs with an incidence of 1:3000 to 1:4000.Variation of incidence are more likely to the kind of screening method than

to ethnic affiliation, or as a result of iodine deficiency thyroid disorders **(Buyukgebiz 2013).** For reasons that remain unclear, Congenital hypothyroidism affects more than twice as many females as males and there is an increased risk in infants with Down's syndrome **(Rose and Brown 2006)** and **(Roberts, Moore et al. 1997).**

Screening programs led to the effective early identification and treatment of infants with Congenital hypothyroidism and have eradicated the severe neurodevelopmental disorder resulting from delayed diagnosis**(Léger, Olivieri et al. 2014) .**

Thyroid function of the neonate can be affected by the mother's thyroid status by way of placental transfer. While TSH is not transferred from the mother, small amounts of thyroxine (T4) and triiodothyronine (T3) do cross
the placental barrier **(Simpser and Rapaport 2010)** .

Infants with Congenital hypothyroidism are lethargic, constipated, feed slowly, and sleep more, often needing to be stimulated to feed. They, may feel cool to touch, may be hypotonic with slow reflexes, may have a hoarse cry and immaturity of hepatic glucuronyl transferase may cause prolonged jaundice **(Kaye 2006)**.Thyroid hormone replacement is treatment for Congenital hypothyroidism **(Simpser and Rapaport 2010)**.

2. Phenylketonuria:

Phenylketonuria is an autosomal recessive inborn error of phenylalanine metabolism if untreated or undiagnosed, the neurotoxic effects of excess phenylalanine can lead to impaired postnatal cognitive development, occurring in approximately 1:15,000 people, **(El-Metwally, Yousef Al-Ahaidib et al. 2018).** High rate of consanguinity relatives increase the risk of the disease**(Ganji, Naseri et al. 2018)**. At birth, Infants with phenylketonuria appear normal, many have fair

hair and skin, blue eyes, vomiting, an eczema- like rash, irritability, active muscle tendon reflexes and a mousy odor in the urine. later, seizures ,mental retardation and microcephaly happens **(Thijeel 2013).**The occurrence of phenylketonuria varies among ethnic groups and geographic regions worldwide **(Hardelid, Cortina-Borja et al. 2008).** For example ,The incidence of phenylketonuria in Caucasian populations is between one patient in 10,000 and one patient in 15,000 people. The treatment of phenylketonuria is phenylalanine-restricted diet ,which should be started as soon as diagnosis is confirmed, to decrease phenylalanine levels in the body(plasma, brain and urine), because phenylalanine is not synthesized endogenously **(Thijeel 2013)**.

3. Galactosemia*:*

Galactosemia is an inborn error of galactose metabolism and autosomal recessive disorder that results from a deficiency in one of three enzymes, Galactokinase(GALK),galactose-1-phosphate uridyltransferase (GALT) or uridine diphosphate galactose 4'epimerase(GALE)**(Anderson 2018).**

There are three basic forms of GALT deficiency: **(Berry 2012)**

1) Classic galactosemia
2) Clinical variant galactosemia
3) Biochemical variant galactosemia.

The incidence galactosemia of widely varies worldwide, with an estimated incidence of 1:19,000 to 1:44,000 in Europe (with a higher incidence in the Irish Traveller population) and the USA **(LindseyWelling, Bernstein et al. 2016)**. The Galactosemia symptoms seen in the early stage during the feeding of breast milk. The early symptoms are; seizures, vomiting, hypoglycemia, jaundice (yellow skin and the white eyes), the liver enlargement, failure to gain weight, irritability, poor feeding, lethargy and diarrhea **(Ali, Khan et al. 2017)**.

Reproductive problems caused by premature ovarian failure occur in females with classic galactosemia **(Bosch 2006).** While galactosemia morbidity and mortality is amenable to management by galactose-restricted diet, the chronic morbidity in classic galactosemia in not amenable to management by diet.

The earlier the institution of galactose-restricted diet the better the prognosis, as children with galactosemia are challenged in their early days by life-threatening amounts of galactose, given that breast milk is rich in lactose that is a disaccharide composed of galactose **(Kotb, Mansour et al. 2018).**

Evaluation of programs

Evaluation of any program is a systematic and objective assessment of an on-going or completed program, its design, implementation and results. The aim is to regulate the relevance and fulfillment of objectives, development efficiency, effectiveness, impact and sustainability **(Kahan 2008)**. So evaluation of any Program significant to recognize, verify or increase the effect of products or facilities on customers or clients, Better delivery mechanisms to be more effective and confirm that you're doing what you think you're doing**(McNamara 1998).**

Newborn screening program was assessed in different areas of the world with variation in results **(Ganji, Naseri et al. 2018), (Al Hosani, Salah et al. 2014), (Hettiarachchi 2014), (Ltd 2014), (Dabbous, El et al. 2008).** Including one study conducted in Baghdad by Alkhazrajy and Hassan in 2014**(Alkhazrajy and Adnan 2016**). This study aimed to assess the NBS program implementation in Karbala governorate within 5 year period.

Objective of study

- To assess the neonatal screening program results in Karbala governorate between 2013-2018.
- To estimate the incidence of congenital hypothyroidism, phenylketonuria and galactosemia in Karbala governorate.

CHAPTER

TWO

METHODOLOGY

2-1 Study design:

The study was a biometeric study.

2-2 Study setting:

The data collection was carried out in Karbala health directorate which includes four Sectors these are Center Sector, Primary health care sector in Husseiniya , Alhur Sector and Primary health care sector in al-hindiyah, all these Sectors involved in study at Karbala governorate, Iraq. The data collection was done between the 1st April 2013to the 1st April 2018.

2-3Study sample:

All newborns records from all four primary health Sectors (Center Sector, Al-Husseiniya, Alhur, and Al-Hindiyah health Sectors) at the beginning of program in April 2013 till first of April 2018 were including in this study.

2-4 Data source:

It includes records files of results of all infants involve in the screening programs in all four primary health Sectors (Center sector, Al-Husseiniya , Alhur, and Al-Hindiyah health Sectors).The records of all registered screened neonates from the beginning of program at April 1, 2013 to March 31, 2018 were reviewed and included. The information about the number of lived birth for each year obtain from ministry of health annual statistical report for the years 2014- 2017(MOH 2014, MOH 2015, MOH 2016, MOH 2017) and from Statistics section in Karbala health Directorate regarding the period of April-December 2013, and January-March 2018.

Data collection Tools and Instruments

In Iraq, neonatal screening still novel, and families mainly bring their neonates for the vaccination, and most of them come within the second to third week of life. The health care providers will explain the screening test and its importance to the families of babies and encourage them to participate in the program.

- Records of screened of newborns(Central Public Health Laboratory in Karbala): the total number of screened newborns(153,281) for each year was taken from Central Public Health Laboratory in Karbala. Recording of the needed information about the infant, which called demographic date on the filter paper cards and the blood specimens put on specific circle found in this card (appendix-A)
- Number of live births from Iraqi ministry of health (MOH) annual statistical report
- Laboratory results for phenylketonuria, Congenital hypothyroidism and galactosemia screening taken from Central Public Health Laboratory while the result of confirmatory test take place outside Iraq(Jordan country) by tandem mass spectrometry. Positive screening tests results detected then the test is repeated in the same(F.P), if it is still positive then confirmatory tests Should be performed to confirm Congenital hypothyroidism by tacking blood serum sample while in case of phenylketonuria and galactosemia a new (F.P) is used for confirmation. The screening and confirmatory test for Congenital hypothyroidism takes place in Central Public Health Laboratory.
- The number of children who diagnosed with confirmatory test and loss to follow up and number of children with regular visit to hospital were obtain from Karbala teaching hospital for children(Screening program unite) and Al Hindia General hospital.

- Laboratory technique: primitive screening test for Congenital hypothyroidism was done by measure TSH level by using DELFIA technique. When the primitive screening results are abnormal, blood should be collected by venipuncture as soon as possible to confirm the abnormal screening results by using mini vidas system. For screening(Primitive) test : nTSH (F.P) is measure, and for confirmatory test: serum nTSH and T4 are measured. The result interpreted according to the following reference value:

Test	Age	Reference value
TSH	1 – 4 Days	1-39 µ|U/ml
	1 week – 5 months	1.7-9.1 µ|U/ml
	5 months – 20 years	0.7 – 6.4 µ|U/ml
T4	1 – 3 Days	152-292 nmol/ml
	1 – 4 week	126-212 nmol/ml
	1 – 4 months	93-189 nmol/ml

In the screening method for phenylketonuria, for screening test: n phenylalanine (F.P) is measured. For confirmatory test: n phenylalanine, Tyrosine and phenylalanine/ Tyrosine ratio (F.P) are measured. The result interpreted according to the following reference value :

Test	Reference value
n phenylalanine	10-150 µM/L
Tyrosine	10 -200 µM/L
Phenylalanine/ Tyrosine ratio	0.28-3.0

Screening method for galactosemia: in screening test: n total galactose (F.P) is measured. But for confirmatory test: n total galactose, (GALT) G 1-p uridyl transferase (F.P) is measured. The result interpreted according to the following reference value:

Test	Reference value
n total galactose	< 9.9 mg/dl
(GALT) G 1-p uridyl transferase)	>3.0 U/g Hb

(Adopted by Central Public Health Laboratory in Karbala)

2-5 Statistical analysis:

The following equation was used:

$$1.\ \text{Coverage rate} = \frac{\text{Number screened}}{\text{Number should be screened}} * 100$$

$$2\text{- Incidence for each disease} = \frac{\text{New case for each disease}}{\text{Number of lived birth}} * k$$

$$3\text{-Percentage of neonate with positive Screening test} = \frac{\text{Number of positive screening test}}{\text{Number screened}} * 100$$

$$4\text{- Positive predictive value} = \frac{\text{Number of positive confirmatory test}}{\text{Number of +ve screening test}} * 100$$

$$\text{5- Detection ability} = \frac{\text{Number of positive confirmatory test}}{\text{Number screened}} * 100$$

Data of patient records were entered and analyzed using the statistical package for social sciences(SPSS) version 23. Specific program indicators include age at sampling, time taken to deliver the specimen to Central Public Health Laboratory, elapsed in lab and neonate age when treatment was initiated and compared to international standard**(Simpson, Randall et al. 1997).**

2-6 Ethical and administrative approval:

An official permission at 27April 2018 obtained from Family and Community Medicine department of medical college of Kerbala University, also from Research Ethical Committee in Karbala Health Directorate, from Central Public Health Laboratory, from Karbala Teaching Hospital for Children and verbal consent was taken from Al Hindai General Hospital (appendix-B).

CHAPTER THREE RESULT

Result:

The total number of neonate that should be screened in period between April 2013 to 1st April 2018 were 213615 neonates while the neonate that screened were 153281 neonates, the total coverage of screening program was 71.7%. The highest coverage rate was in 2015 (84.6%) and the lowest coverage was in first years of program (61%), all this and more was showed in table1.

Table 1-coverage rate of screened neonate for 5 consecutive years.

Years	No. should be screen	No. of screened	Coverage rate %
From 1st April 2013	31243	19071	61%
2014	43943	35244	80.2%
2015	41894	35453	84.6%
2016	42757	28565	66.8%
2017	43296	27264	62.9%
To 1st April 2018	10482	7684	73.3%
Total	213615	153281	71.7%

From all neonates screened, the total number of positive screening test since 1st April 2013 to 1st April 2018 for three screened disease were 681. All those invited by phone calling to do second confirmatory test, only 25 family was not inform because the parent may give wrong phone number or no answer. From those who inform about primitive test result 418 families respond to call and done the confirmative test, 238 families were not responding to call. From those who response to call and done the confirmatory test, 191 neonates had positive confirmatory test, 12 neonates had borderline result and 215 neonates had negative confirmatory test. Those who had positive confirmatory test, 26 neonates not start treatment at Karbala Teaching hospital for Children while 165 neonate start

treatment, the remainder number which represent 30% from coverage rate either go to the private clinic outside hospital or take the treatment from another side. All this showed in figure1.

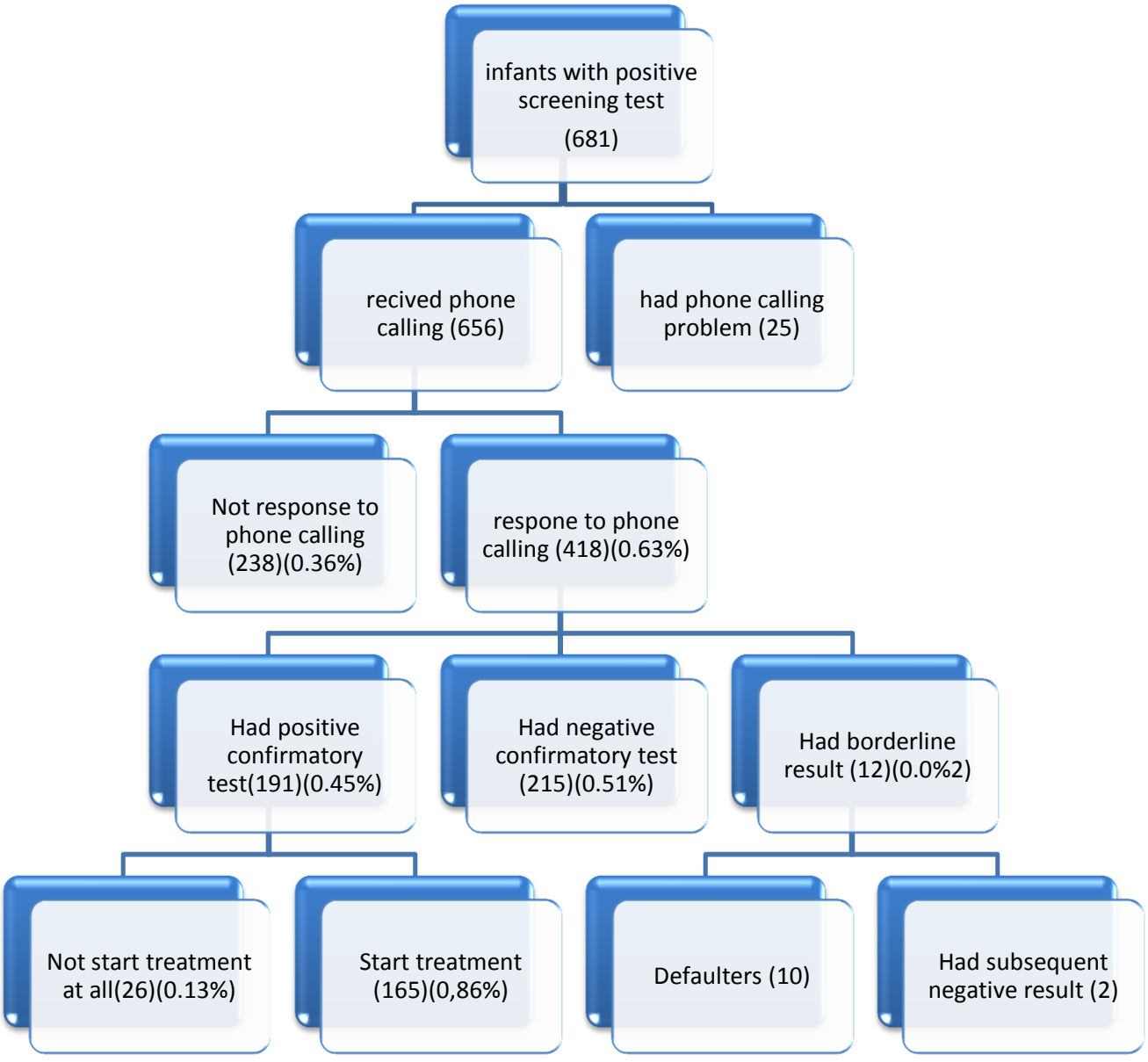


Figure 1- Flow chart to show data sets available for the program evaluation.

In the following table, note the overall incidence of congenital hypothyroidism was 6.5:10000 (1:1538), and there is increased incidence between 2014 and 2016.

Table 2- Distribution of the sample by screening, confirmatory tests and incidence of congenital hypothyroidism in 5 consecutive years.

Congenital hypothyroidism	+ve ST	% of +ve ST	+ve CT	DA%	PPV	Incidence/10000
2013	43	0.22%	10	0.052	23.2%	3.2/10000
2014	88	0.24%	34	0.096	38.6%	7.7/10000
2015	69	0.19%	33	0.093	47.8%	7.8/10000
2016	78	0.27%	32	0.112	41%	7.4/10000
2017	51	0.18%	24	0.088	47%	5.5/10000
To 1st April 2018	11	0.1%	6	0.078	54.5%	5.7/10000
Total	340	0.22%	139	0.090	40.8%	6.5:10000(1:1538)

ST= screening test, CT= confirmatory test, PPV= Positive predictive value, DA=Detection ability

The number of neonate with positive confirmatory test for congenital hypothyroidism and male was 74(53.2%) while the number of neonate with positive confirmatory test and female was 65(46.8%) this showed in figure 2. The male to female ratio was 1.1:1(P:0.37).

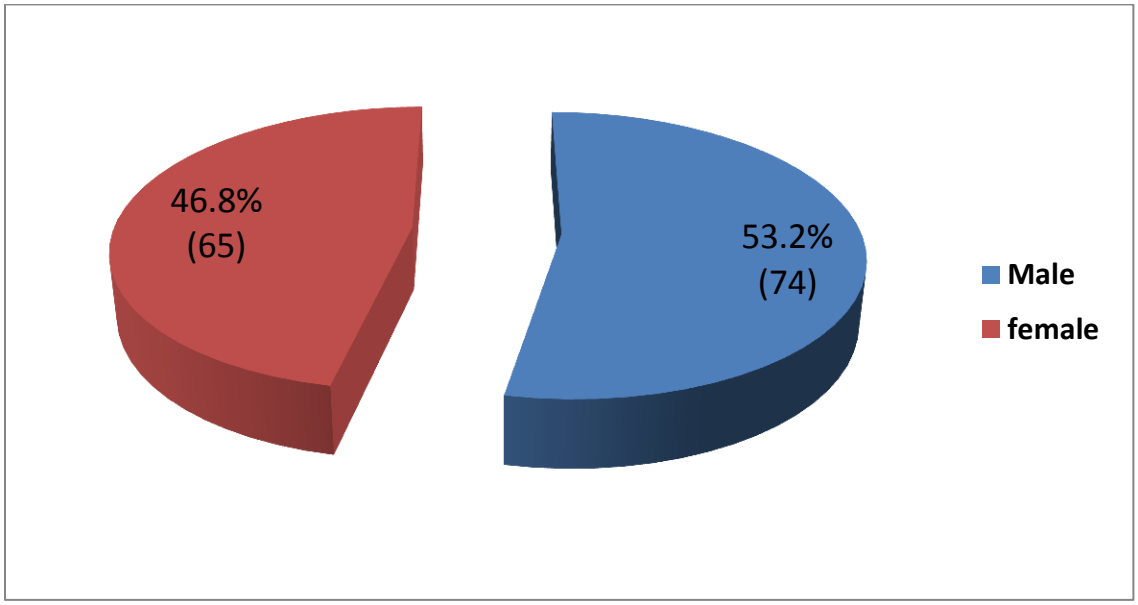


Figure 2 gender distribution among congenital hypothyroidism.

The total numbers of neonates with positive screening test for phenylketonuria were 56 neonates, while those with positive confirmatory test were 29 neonates. And the positive predictive value (PPV) of was 51.8%, the overall incidence of phenylketonuria was 1.3:10000 (1: 7692).

Table 3- Number and percentage for screening and confirmatory test and incidence for Phenylketonuria in 5 consecutive years.

Phenylketonuria	+ve ST	% of +ve ST	+ve CT	DA%	PPV	Incidence/10000
2013	10	0.052%	5	0.026	50%	1.6/10000
2014	20	0.056%	8	0.022	40%	1.8/10000
2015	11	0.031%	6	0.016	54.5%	1.4/10000
2016	5	0.017%	3	0.010	60%	1.6/10000
2017	8	0.029%	6	0.022	75%	1.3/10000
To 1st April 2018	2	0.026%	1	0.013	50%	9.5/10000
Total	56	0.036%	29	0.018	51.8%	1.3:10000(1: 7692)

Table 4- Number and percentage for screening and confirmatory test and incidence for galactosemia in 5 consecutive years.

Galactosemia	+ve ST	% of +ve ST	+ve CT	DA%	PPV	Incidence/10000
2013	47	0.24 %	1	0.005	2.1%	3.2/10000
2014	111	0.31 %	11	0.031	9.9%	2.5/10000
2015	69	0.19 %	4	0.011	5.7%	9.5/10000
2016	42	0.14 %	2	0.007	4.7%	4.6/10000
2017	13	0.047 %	4	0.014	30.7%	9.2/10000
To 1st April 2018	3	0.039 %	1	0.013	33.3%	9.5/10000
Total	285	0.18 %	23	0.015	8%	1:10000(1:9345)

The result in the above table:

1) Only 23 cases were confirmed as Galactosemia.
2) More cases were in year of 2014.
3) Among 285 screened newborn only 8% had Galactosemia with incidence rate of 1/10000.
4) There is large number of false +ve in screening test.

The mean age at first sampling for those with positive screening test was11.4±7.8 days and median was 10 days. The percentage of neonate that done the first sampling at age ten days and younger was calculated for Congenital hypothyroidism years and this showed in figure 3. According to international standard the percentage should be 100%.

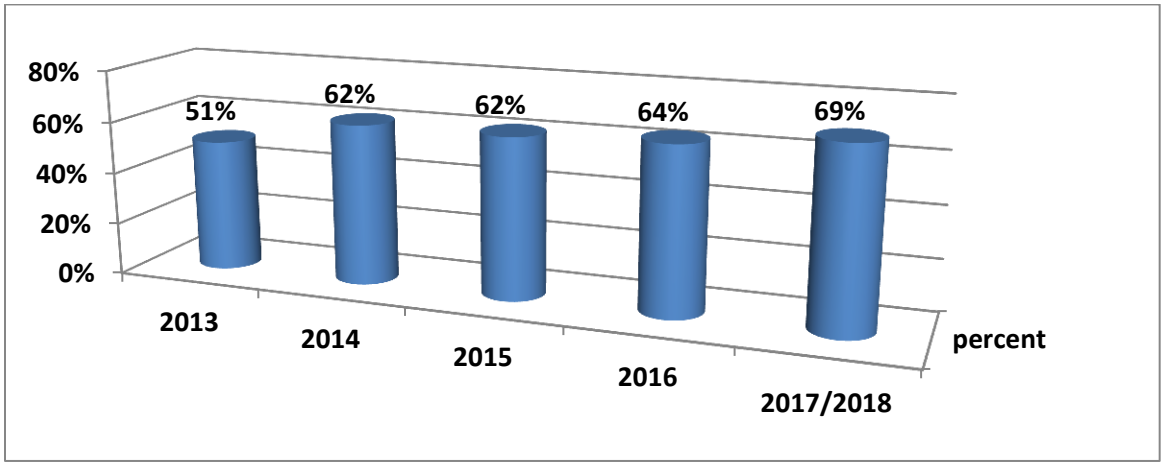


Figure 3 The percent of neonates that did the first sampling at age of ten days and younger for each year.

The percentage of screening card samples received by the laboratory within 6 days of being taken was also measure for each year and this showed in figure 4. According to international standard the percentage should be 95%.

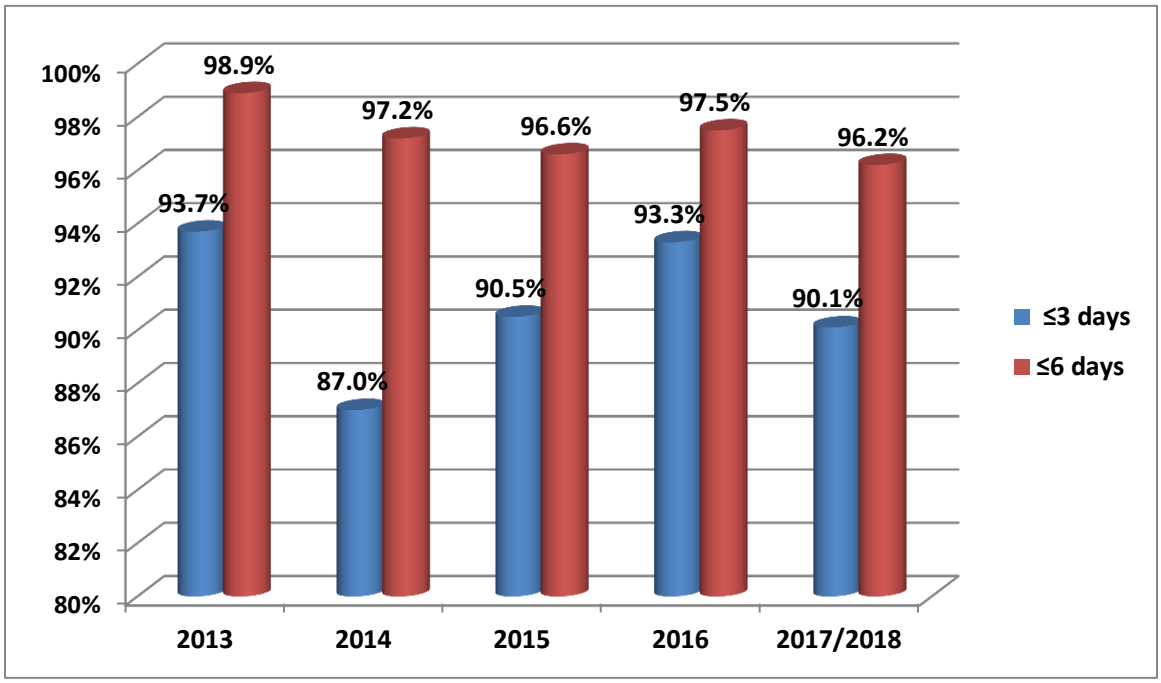


Figure 4 The percent of screening card samples received by the laboratory within 6 days of being taken for each years.

The percent of result to be available within four working days from date of received to lab was also measure for each year and this showed in figure 5. According to international standard the percentage should be 100%.

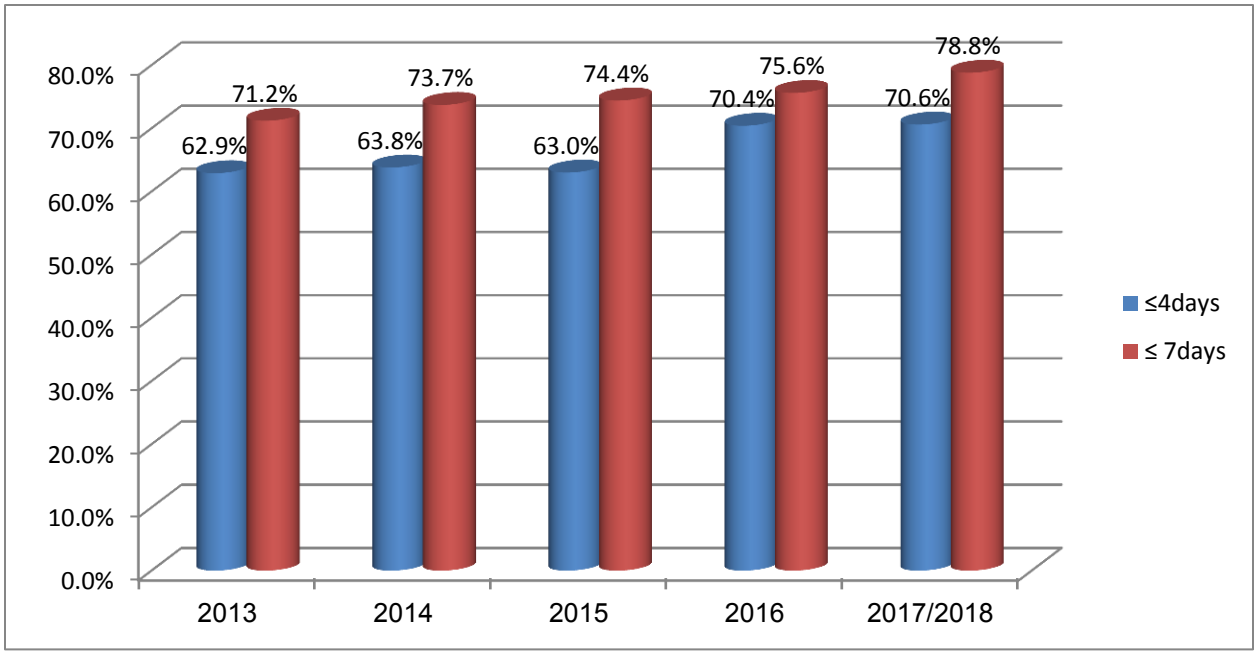


Figure 5 The percent of available results within four working days for each year.

The mean age at second sampling was26.5 ±9.8 days and median was 23 days. The percentage of neonates who diagnosed and received appropriate treatment by 28 days of age for each year was showed in figure 6. According to international standard the percentage should be 95%.

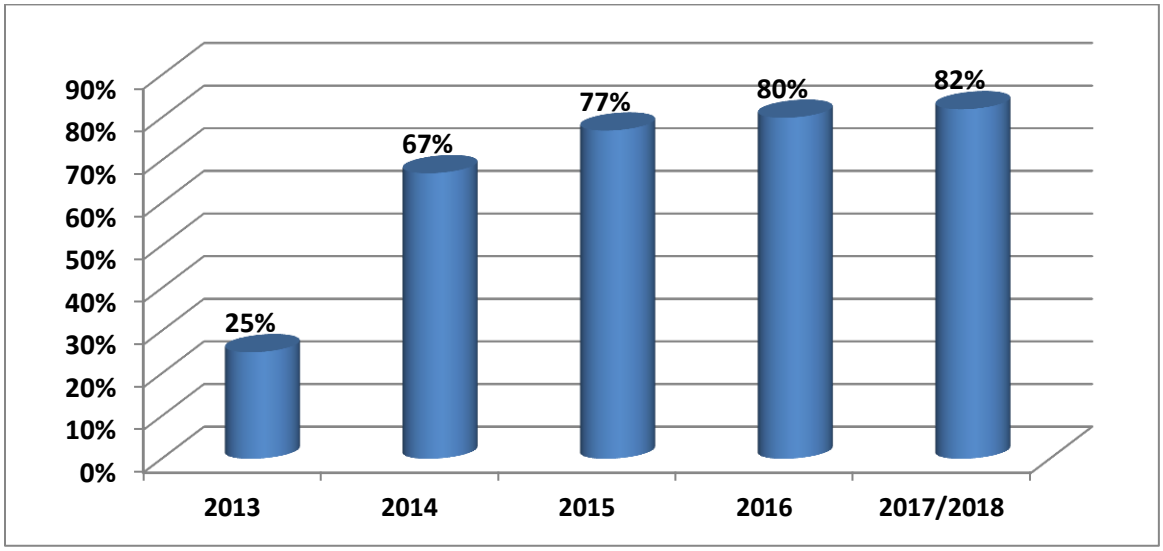
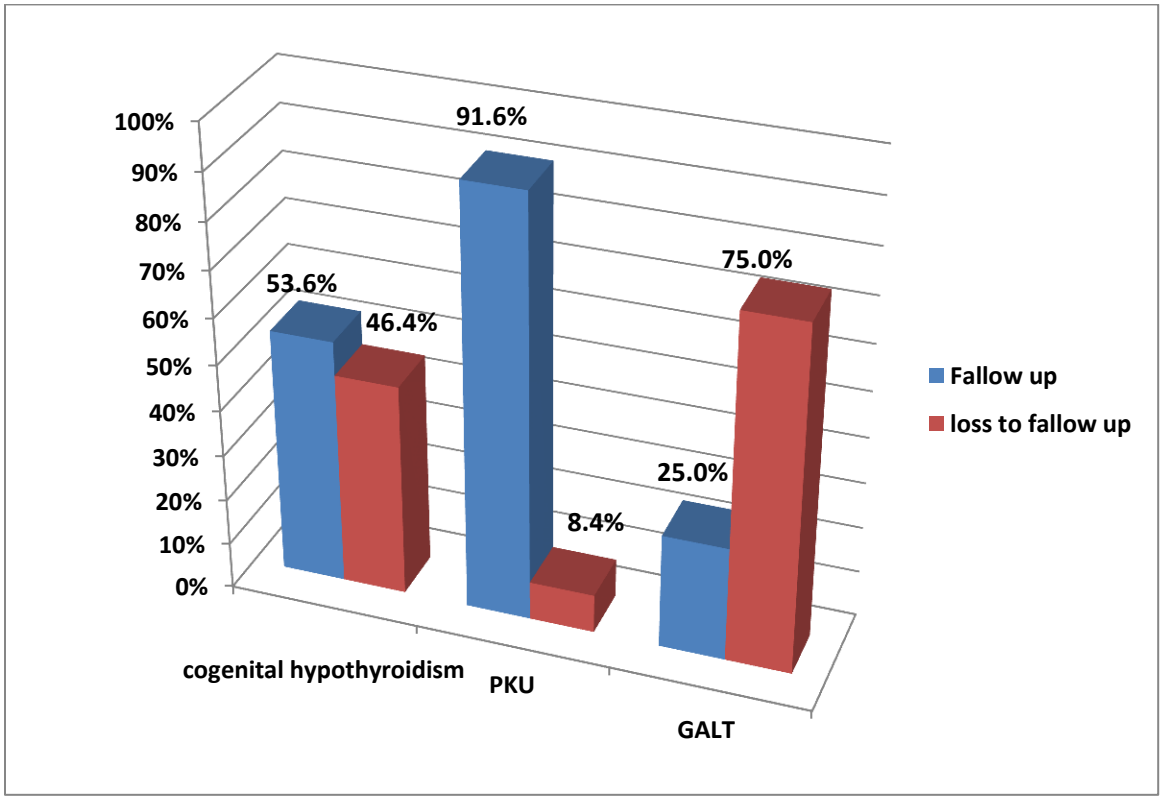


Figure 6 The percent of neonates who diagnosed and received appropriate treatment by 28 days of age for each year.

The numbers of children with regular follow up for congenital hypothyroidism were 67(53.6%) while those children those losses to follow up were 58 (46.4%). The numbers of children with regular follow up for phenylketonuria were 22(91.6%) while those children those losses to follow up were 2 (8.4%). The numbers of children with regular follow up for galactosemia were 4(25%) while those children those losses to follow up were 12 (75%) figure 7.



GALT= Galactosemia

Figure 7 The percent of Congenital hypothyroidism, phenylketonuria, galactosemia children according to follow up in hospital.

CHAPTER

FOUR

DISCUSSION

Discussion

In this study, which is the first study in Karbala governorate about NBS, the universal coverage of newborn screening program was 71.7%, this rate coverage in compare to international standard (99%) is suboptimal **(Rose and Brown 2006)**. The lowest coverage was found at start of program at 2013 (61%), which was less than nine months. Then at 2014 and 2015 the coverage rate increase to 80.2%, 84.6% for that year respectively. The sharp decline in coverage rates percentages between 2015 and 2016 from 80s to 60s was probably due to the reduction of the upper age limit in inclusion criteria to one month from two month at starting of the program (appendix-C). Other cause for the sharp decrease is that the program had faced time of pausing due to lack of lab materials in 2016 and 2017 for 2-3 months in each year.

However, this rate is higher than a study done at 2014 in Baghdad city where the coverage rate was 66% **(Alkhazrajy and Adnan 2016)**. In Alexandria\ Egypt program the coverage rate was 49.4% in 2001 and increase to 82.7% in 2005**(Dabbous, El et al. 2008).** While a study done in the United Arab Emirates (UAE) the rate of coverage neonatal screening increased from 50% in 1998 to 95% in 2010 **(Al Hosani, Salah et al. 2014).** In Saudi Arabia (Al-Madina Al-Munawara region) the screening program coverage was nearly 97% of the total infants born in Madina region over 10 years**(Al-Maghamsi, Al-Hawsawi et al. 2002)**, in Sri Lanka the coverage rate reach 99.9% in 2014 **(Hettiarachchi 2014)**. Anyhow this result or that in Baghdad is not unexpected and might even considered good as a newly introduced program. If take in account the status or context of the health system and health services in Iraq which suffer many crises. Also it could be attributed to the low percentage of the

first visit of neonate to(PHC)and lower awareness and knowledge of families about NBS program.

Adding to that the program had some periods of delay due to lack of lab materials, or long holidays in Karbala during the Million visits hosted in the city including the biggest annual mass gathering in the world "the Arbaeen Visit of Imam Hussein **(Abutiheen 2014)**where most Primary health care centers stopped its routine work for several days to two weeks during Arbaeen visit. While other explanation for this shortage in coverage is the high birth rate in Karbala which ranged between 36.1 – 38.7/ 1000 population within years of study **(MOH 2014, MOH 2015, MOH 2016, MOH 2017).**

For Congenital hypothyroidism, the overall incidence was 1:1538. In compare to other countries as following table:

Location	Incidence rate	Name of first author , year
Iran	2/1000	**(Veisani, Sayehmiri et al. 2014)**
Turkey	1/2736–1/2326	**(Simşek, Karabay et al. 2003)**
Greek Cypriot	1/1800	**(Skordis, Toumba et al. 2005)**
Italy	1/1446	**(Corbetta, Weber et al. 2009)**

This difference in the incidence may be due to different TSH cutoff values, and may also due to regional different in the levels of iodine deficiency.

The result of program for congenital hypothyroidism revealed that male to female ratio was 1.1:1. There is no statistical difference between male to female (P:0.37) which is not significant. There are varying findings about congenital hypothyroidism occurrence risk with regard to gender. Some researchers have showed that congenital hypothyroidism occurrence is associated with boy gender**(Dorreh, Chaijan et al. 2014)** and **(Zeinalzadeh and Talebi 2012).** whereas others have found an

increased risk of Congenital hypothyroidism in girls**(Medda, Olivieri et al. 2005)** and **(Abdelmoktader 2013)** or no variation **(Ghafoor, Mohsin et al. 2013)** and **(Malik and Butt 2008).** This difference probably due to many factors including, differing statistical methods, study design, sample size, different prevalence across the populations and chance may be related to variation in the association between gender and Congenital hypothyroidism occurrence.

The program had low positive predictive value (PPV) (40.8%) for congenital hypothyroidism The result of the program was a round similar to Iran program Low (33%) (PPV) **(Karamizadeh, Saneifard et al. 2012)**. In this study, the program had relatively high positive screening test percentage (0.22%) In compare to Iraqi study that done in Baghdad pooled positive screening test percentage (0,047%) **(Alkhazrajy and Adnan 2016)** while Macedonia have positive screening test percentage (0.18%) **(Anastasovska, Koviloska et al. 2014)**.The cause behind this may be related to transient abnormalities of thyroid function in the newborn period.

Based on finding of this study, the total incidence of phenylketonuria in Karbala province was 1: 7692. This ratio varies in different countries:

Location	Incidence rate	Name of first author , year
Iran	1:6662	**(Ganji, Naseri et al. 2018)**
Arabian countries	more than 1:5000	**(Williams, Mamotte et al. 2008)**
Turkey	1:2600	**(Williams, Mamotte et al. 2008)**
Brazil	1:8690	**(Ramalho, Ramalho et al. 2014)**
Finland	1:200000	**(Williams, Mamotte et al. 2008)**
Japan	1:125000	**(Williams, Mamotte et al. 2008)**

The cause behind this different may be due to hereditary factors, awareness of families, high consanguinity and different in coverage rate of testing which use to diagnose the disease.

For phenylketonuria, the program had pooled positive screening test percentage (0.036%) is high in compare to other Iraqi study that done in Baghdad pooled positive screening test percentage 0.014% **(Alkhazrajy and Adnan 2016)**. In another hand ,this study had PPV (51.8%) in compare to PPV in United Arab Emirates was 13.7%**(al-Hosani, Salah et al. 2003).**

Regard the galactosemia, the overall incidence was 1:9345and in compare to the other countries:

Location	**Incidence rate**	**Name of first author , year**
Southern Iran	1:600**0**	**(Senemar, Ganjekarimi et al. 2011)**
White Americans	1:47000	**(Senemar, Ganjekarimi et al. 2011)**
United Kingdom	1:70000	**(Senemar, Ganjekarimi et al. 2011)**
Ireland	1:23000	**(Senemar, Ganjekarimi et al. 2011)**

The incidence of galactosemia in Karbala and Southern Iran was being higher than that in other countries; this might be because the number of consanguineous marriages in these countries is higher than other populations.

For galactosemia , the pooled positive screening test percentage was high (0.18%) in compare to other Iraqi study was 0.011% **(Alkhazrajy and Adnan 2016)** %). But on reviewing the table for these percentage from beginning of program till 1st April 2018 there were improvement in positive screening test percentage from 0.24% in 2013 to 0.039%

2018,this is might be increasing cutoff value of n total galactose (normal value< 9.9 mg/dl) from 12 mg/dl at the beginning of program to >20mg/dl that used in screening test of galactosemia in addition to that and galactose concentration influence with storage and transportation conditions . The PPV was to low (8%), in compare to other International studies such as in Philippines, PPV was (16.7%), Sweden (64.3%) and USA (87.0%) **(Ltd 2014).** This low PPV as mentioned previously, probably because difference in the cut-off value, different technique that used in every country but in general theirs also improvement for every year in positive predictive value from 2.1% in 2013 to 33.3% in 2018. The positive screening test percentage it's still high, the high number total galactose in the screening tests may be caused by deficiency of any one of the other two enzymes causing galactosemia (GALK and GALE) that are not included in this screening program, so we need to refer this cases to pediatric metabolic specialist must be done in these cases to measure the level of the other two enzyme (Galactosemia variants).

The mean age at first sampling for those with positive screening test was 11.4 ±7.8 days and median was 10 days and the mean age at second sampling was 26.5 ±9.8 days and median was 23 days. But, other countries had extremely lesser day i.e., at United Arab Emirate the first sampling was in 5.3 day and the second sampling was in 15.4 days **(al-Hosani, Salah et al. 2003)** While in Sri Lanka the median age of the program at screening sample was (1.0 day) and mean age at second sampling was 23.0 **(Hettiarachchi 2014)** The cause may be referral to different in educational levels and health system between countries.

The appropriate age of sampling in the NBS was a matter of debate. The optimum age of sampling on various causes as, the number of

disorders investigated for and screening technique **(Dabbous, El et al. 2008))**.

Timeliness in NBS, is a time sensitive process in which a delay in specimen collection, transport, testing, and/or reporting of results could lead to serious consequences for a newborn that is affected by one of the disorders currently screened**((NewSTEPs) 2016)**. A comparison of timeliness of the screening program indicators in this study shows that some of newborn screening program indicators was improved between 2013 and 2018 like elapsed in laboratory for less than 4 days, from 62.9% in 2013 to 70.6% in 2017/2018 this improvement may be due to the training provided to laboratory technicians and adding new laboratory staff. Also the age at start treatment before 28 days from 25% in 2013 to 82% in 2017/2018 this may be due to the improvement in laboratory performance and increase education about program among health care provider. The speed of sampling arrived to laboratory within 6 days was above the international standard since 2013, this probably due to speed of vehicle delivery of specimens to laboratory 2-3 time per week. While the age at first sampling was nearly the same between 2013 to 2015, thereafter some improvement from2016-2018, but still low and below the international standard, this may be due to low percentage first visit to PHC after birth associated with availability of BCG vaccine. The parents don't bring their neonates earlier for screening ,So emphasize and encourage health care providers on families about importance of newborn screening.

About children follow up in hospital, the high percentage of loss to follow up in case of galactosemia may be due to unavailability of special milk formula for those children and some of families take their children for private clinic and don't bring their for hospital for follow up or the

child are die from complication of their disorder while the cause of high follow up in case of phenylketonuria may be due to availability of special milk formula for those children. For Congenital hypothyroidism about half of children were lost, the cause may be due to unavailability of special drug for that disease and as mentioned previously some of families take their children for private clinic and don't bring their for hospital other half who had regular follow up to hospital was follow for checkup investigations.

Limitations of study

1-The data collection time was short.

2-There was no computerized data base in Central Public Health Laboratory to obtain full information for each sample take.

3-Defaulters were found in every level of evaluation of program this influence on study result.

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CHAPTER

FIVE

CONCLUSION& RECOMMENDATION

Conclusion

- the coverage rate in Karbala Health Directorate was suboptimal compared to the international standard.
- The incidence of three screened diseases was considered as high.
- the overall results of screening test, age of screening sampling, lab performance and follow up were below the international standard.

Recommendation

❖ Increase community awareness through health education about program in form of health Awareness campaigns, perinatal and antenatal health education even in premarital state; provide information sheet and adequate information given by midwife, nurse and health care providers to parents on program, proper time of sampling and important of disease.

❖ Better recall system for defaulters to take second sample which is considered very important for confirmation of disease.

❖ Reassess the cut-off values used in this program which influence on false positive screening test results.

❖ Increase training for laboratory staff to improve their performance and adding new staff with provision of laboratory materials, reactivation of referral system to reduce the missed cases and provide drugs and special milk formula to decrease loss to follow up.

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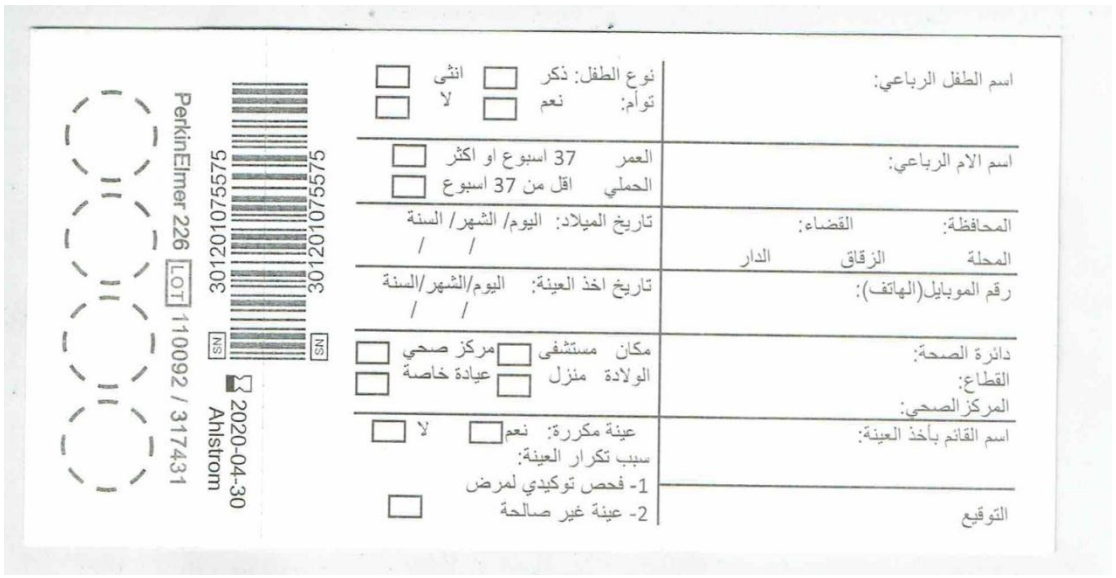
Appendix A


اسم الطفل الرباعي:
نوع الطفل: ذكر انثى
توأم: نعم لا
اسم الام الرباعي:
العمر 37 اسبوع او اكثر
الحملي اقل من 37 اسبوع
المحافظة: القضاء:
المحلة الزقاق الدار
تاريخ الميلاد: اليوم/ الشهر/ السنة
/ /
رقم الموبايل(الهاتف):
تاريخ اخذ العينة: اليوم/الشهر/السنة
/ /
دائرة الصحة:
القطاع:
المركز الصحي:
مكان الولادة مستشفى مركز صحي منزل عيادة خاصة
اسم القائم بأخذ العينة:
عينة مكررة: نعم لا
سبب تكرار العينة:
1- فحص توكيدي لمرض
2- عينة غير صالحة
التوقيع
30120107575
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2020-04-30
Ahlstrom
PerkinElmer 226 LOT 110092 / 317431

Appendix B

Holy Karbala governorate
Karbala Health Directorate

محافظة كربلاء المقدسة
دائرة صحة كربلاء المقدسة
مكتب المدير العام
مركز التدريب والتنمية البشرية
وحدة البحوث
العدد/ ١٢٧
التاريخ/ ٢٧/ ٢/ ٢٠١٨

إلى/جامعة كربلاء/ كلية الطب
الموضوع/تسهيل مهمة

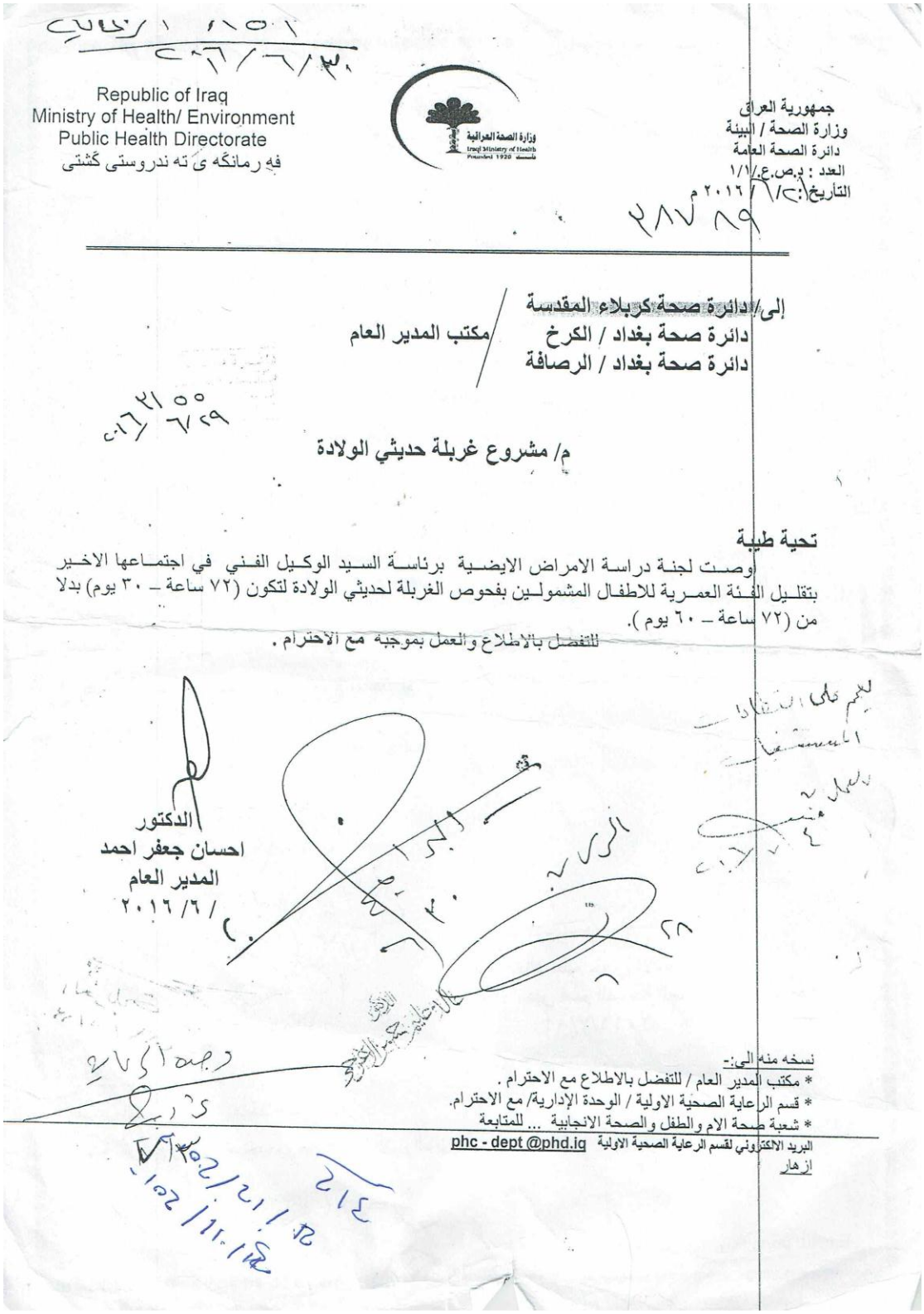
السلام عليكم...
كتابكم ذي العدد ٧١٩ في ٢٠١٨/٢/٢١
لا مانع لدينا من تسهيل مهمة طالبة الدراسات العليا (فاطمة محمد جابر)لانجاز بحثها الموسوم :
((تقييم برنامج الغربلة لحديثي الولادة في محافظة كربلاء المقدسة عبر ٥سنوات))٢٠١٨
Assessment of neonatal screening program over 5 years in karbala governorate (2013 / 2018)
في مؤسستنا الصحية المبينة ادناة على ان يكون المشرف العملي على البحث (د. محمد فراس خضر)
علما أن دائرتنا لا تتحمل أي نفقات مادية ...مع الاحترام

المؤسسات
١. مستشفى كربلاء التعليمي للاطفال
٢. قسم الصحة العامة – مختبر الصحة العام
٣. قطاع المركز

الطبيب الاختصاص
معتصم غازي حسون المحنا
معاون المدير العام
٢٠١٨/ ٣/

نسخة منه الى:
مستشفى كربلاء التعليمي للاطفال / كتابكم المرقم ١٣١٣ في ٢٠١٨/٣/٢٧ لاتخاذ مايلزم وحسب الضوابط مع الاحترام .
قسم الصحة العامة – مختبر الصحة العام / كتابكم المرقم ١٥٥٩ في ٢٠١٨/٣/٢٧ لاتخاذ مايلزم وحسب الضوابط مع الاحترام .
قطاع المركز / كتابكم المرقم ١٩٦٥ في ٢٠١٨/٣/٢٧ لاتخاذ مايلزم وحسب الضوابط مع الاحترام.
-مركز التدريب والتنمية البشرية -مع الأوليات
إسراء .....

العنوان / كربلاء المقدسة – حي الحسين(ع) – قرب دائرة كاتب العدل & رقم الهاتف / ٠٣٢٣٢٨٠٠٢
البريد الالكتروني/ train.centerkh@Yahoo.com & Email/ الموقع على فيسبوك/مركز التدريب والتنمية البشرية/صحة كربلاء



Republic of Iraq
Ministry of Health/ Environment
Public Health Directorate
فەرمانگەی تەندروستی گشتی

وزارة الصحة العراقية
Iraqi Ministry of Health
Founded 1920

جمهورية العراق
وزارة الصحة / البيئة
دائرة الصحة العامة
العدد : م.ص.ع/١/١
التاريخ: ٢٠١٦ م

إلى/ دائرة صحة كربلاء المقدسة
دائرة صحة بغداد / الكرخ
دائرة صحة بغداد / الرصافة
مكتب المدير العام

م/ مشروع غربلة حديثي الولادة

تحية طيبة

أوصت لجنة دراسة الامراض الايضية برئاسة السيد الوكيل الفني في اجتماعها الاخير بتقليل الفئة العمرية للاطفال المشمولين بفحوص الغربلة لحديثي الولادة لتكون (٧٢ ساعة – ٣٠ يوم) بدلا من (٧٢ ساعة – ٦٠ يوم).

للتفضل بالاطلاع والعمل بموجبه مع الاحترام .

الدكتور
احسان جعفر احمد
المدير العام
/ ٦/ ٢٠١٦

نسخه منه الى:-
* مكتب المدير العام / للتفضل بالاطلاع مع الاحترام .
* قسم الرعاية الصحية الاولية / الوحدة الإدارية/ مع الاحترام.
* شعبة صحة الام والطفل والصحة الانجابية ... للمتابعة

البريد الالكتروني لقسم الرعاية الصحية الاولية phc - dept @phd.iq
ازهار

الخلاصـــــــة :-

الخلفية: إن غربلة حديثي الولادة هو برنامج منتظم للصحة العامة لتحديد الأطفال الذين يعانون من حالات يمكن علاجها قبل ظهور الاعراض سريريًا ، أو قبل التعرض لأضرار لا يمكن علاجها. برنامج الغربلة يشمل الرضع في الأيام القليلة الأولى بعد الولادة وحتى شهر واحد من العمر لقصور الغدة الدرقية الخلقي ،فينيل كيتون يوريا وجلاكتوسيميا. لا يمكن اكتشاف الاضطرابات الأيضية بسهولة دون الفحص لأن العديد من الأعراض غير محددة وتبدو كأنها اضطرابات شائعة أخرى. بعض الاضطرابات لا تظهر أي أعراض على الإطلاق حتى حدوث الضرر. في بعض هذه الحالات ، لا يمكن إصلاح الضرر. التحري يعني أنه يمكن تشخيص الاضطرابات الأيضية قبل أن يمرض الطفل.

الغرض من الدراسه :تقييم نتائج برنامج غربلة الأطفال حديثي الولادة في مدينة كربلاء بين 2013-2018 وتقدير حالات قصور الغدة الدرقية الخلقي ، الفينيل كيتون و جلاكتوسيميا في كربلاء وتحديد أي عوائق أو قيود.

طريقة الدراسة: دراسة مقطعية مستعرضة تشمل جميع المواليد الجدد من بداية البرنامج في ابريل 2013 حتى الأول من أبريل 2018. تم الحصول على البيانات من التقرير السنوي لوزارة الصحة ، قسم الإحصاء في مديرية الصحة في كربلاء ، المختبر المركزي للصحة العامة ، مستشفى كربلاء التعليمي للأطفال ، و مستشفى الهندية العام. تم قياس معدل التغطية ، ونسبة اختبار الفحص الإيجابي ، نسبة حدوث المرض، القيمة التنبئية الايجابية ومؤشرات محددة للبرنامج.

النتائج: كان معدل التغطية الكلي 71.7 ٪:مع تحسن بين عامي 2013 و 2018. وكان معدل حدوث قصور الغدة الدرقية الخلقي(1: 1538)ونسبة الذكور إلى الإناث(1: 1.1)، وكان حدوث جلاكتوسيميا (1: 9345)بينما حدوث فينيل كيتون يوريا (1: 7692). المتسربين تم تحديدهم في مراحل مختلفة من البرنامج. بلغ متوسط العمر عند أخذ العينات لأولئك الذين لديهم اختبار فحص إيجابي 11.4 يومًا وكان المتوسط 10 أيام ، وكان متوسط العمر عند أخذ العينات الثاني 26.5 يومًا والمتوسط 23 يومًا. كانت النسبة المئوية للمواليد التي أخذت العينة الأولى منهم في عمر اقل من عشرة ايام بشكل عام متشابهة وقليله مع وجود تحسن قليل بين عامي 2016-2018 ولكنها اقل من المعيار الدولي ،بينما كانت النسبة المئوية لعينات بطاقة الفحص التي

يتلقاها المختبر في غضون 6 أيام من أخذ العينات بشكل عام ايضا متشابهة و فوق المعيار الدولي ،من جانب اخر، فإن النسبة المئوية للنتيجة ستكون متاحة في غضون أربعة أيام من العمل في المختبر من تاريخ الاستلام ونسبة الولدان الذين شخّصوا وتلقوا العلاج المناسب قبل 28 يومًا من العمر قد زادت بين 2013 و 2018 ولكن بشكل عام أقل من المعيار الدولي. ايضا كانت نسبه المراجعة المنتظمة 53.6٪ من حالات قصور الغدة الدرقية الخلقي ، و 91.6٪ فينيل كيتون يوريا و 25٪ للجلاكتوسيميا.

الاستنتاجات والتوصيات: بشكل عام ، كان معدل التغطية اقل من المعيار الدولي وكانت النتائج الإجمالية لاختبار الغربلة ، وعمر الطفل عند أخذ العينات، وأداء المختبر منخفضًا لذلك يقترح زيادة معرفة الاباء والامهات والعاملين في البرنامج حول اهمية برنامج الغربلة والحرص على اهمية الزيارة الاولى بعد الولادة في وقت مبكر

تقييم برنامج الغربلة لحديثي الولادة في محافظة كربلاء المقدسة خلال خمس سنوات /2018

رسالة

رسالة مقدمة الى مجلس كلية الطب – جامعة كربلاء كجزء من متطلبات

نيل شهادة الدبلوم العالي في طب الأسرة

من قبل

فاطمة محمد تاج الدين

بكالوريوس طب وجراحه عامة

اشراف

د. محمد فراس خضر

اختصاص طب الاطفال

أ.م.د علي عبد الرضا ابوطحين

استشاري طب أسرة

2018 م **1440 هـ**