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An Overview on Thalassemia and Challenges during COVID-19

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***Abstract*---**The thalassemia is a group of disorders in which the normal ratio of alpha globin to beta globin production is disrupted due to a disease-causing variant in one or more of the globin genes. This abnormal alpha- to beta-chain ratio causes the unpaired chains to precipitate and causes destruction of red blood cell precursors in the bone marrow (ineffective erythropoiesis) and circulation (hemolysis). Affected individuals with thalassemia have variable degrees of anemia and extramedullary hematopoiesis, which in turn can cause bone changes, impaired growth, and iron overload. The aim and objectives are to describe the basic genetic differences between alpha-thalassemia and beta-thalassemia. Describe the hematologic findings and pathophysiological changes that are associated with beta-thalassemia major. Summarize the etiology of thalassemias and describe the basic genetic differences between alpha-thalassemia and beta-thalassemia. Describe the genetic, hematologic, and clinical differences between alpha-thalassemia trait, hemoglobin H disease, and hydrops fetalis. outline the challenges of thalassemia during Covid 19 crisis. Thalassemia is the most common, inherited, single-gene disorder in the world. Treatment of the inherited blood disorder thalassemia depends upon the level of severity. There are many challenges in the transfusion practice of patients with TM due to fluctuations in the COVID-19 pandemic we encourage all researchers to conducting more study and meta-analysis study among patients suffering from thalassemia during COVID-19 crisis especially during infection, developing complications of disease and post vaccination.

***Keywords*---**Thalassemia, COVID-19, Beta thalassemia, Alpha thalassemia.

Introduction

The thalassemia is a group of disorders in which the normal ratio of alpha globin to beta globin production is disrupted due to a disease-causing variant in one or

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more of the globin genes. There are two types of thalassemia, depending on which type of globin is mutated: alpha- (α-) thalassemia and beta- (β-) thalassemia. α-Thalassemia occurs when one or more of the four α-globin genes are damaged or altered, while β-thalassemia occurs when both β-globin genes are damaged or mutated [1,2]. The severity of alpha and beta thalassemia depends on how many of the four genes for alpha globin or two genes for beta globin are missing. Thalassemia is widely found with different variants in different populations. In 2018, the World Health Organization (WHO) reported that at least 5.2% of individuals worldwide were thalassemia carriers, that approximately 1.1% of couples worldwide were at risk of having children with a hemoglobin disorder, and that 2.7/1,000 conceptions were affected [3]. Worldwide, Hb E–b-thalassemia is one of the most frequent hemoglobinopathies. The incidence of Hb E approaches 60% of the populations in many regions of Southeast Asia. In coastal regions of North America, its prevalence is rapidly growing. a-thalassemia diseases, often considered benign, are now recognized to be more severe than originally reported. Hb H, Hb H–constant spring (CS), and homozygous a-thalassemia affect at least a million people worldwide. California considers Hb H disease a public health problem and has initiated a neonatal screening program for Hb H and particularly Hb H–CS. Homozygous a- thalassemia, usually fatal, is also being more commonly detected [4].

Epidemiology of Thalassemia

Thalassemia affecting population across thalassemic built which extends from the Mediterranean region through Middle East and Sub-Saharan Africa to South and Southeast Asian countries. Nowadays, thalassemia occurs all over the world because of continual migrations of population from these areas to western countries. Thalassemia affects both sexes equally, occurring approximately in 4.4% of every 10,000-live birth and accounting for about 60,000–70,000 children each year who born with different types of thalassemia [5]. It is common in areas with prevalent malaria as thalassemic red cells provide immunity against the parasite. The incidence of thalassemia carriers is high in regions such as Mediterranean, Middle East, Indian subcontinent, Southeast Asia and South China [6].

Etiology of Thalassemia

Thalassemias are caused by an abnormality in the rate of synthesis of the globin chains. This contrasts with the true hemoglobinopathies (e.g., Hb S and Hb C) that result from an inherited structural defect in one of the globin chains that produces hemoglobin with abnormal physical or functional characteristics [4]. Thalassemia inherited as autosomal recessive, to develop thalassemia disease both parents must be affected with or carriers for the disease to transfer it to the next generation. Thalassemia it can caused by mutations or deletions of the Hb genes, resulting in underproduction or absence of alpha or beta chains. There are over 200 mutations identified as the culprits for causing thalassemias. Alpha thalassemia is caused by deletions of alpha-globin genes, and beta thalassemias are caused by a point mutation in splice site and promoter regions of the beta-globin gene on chromosome 11[2]. There are two major types of thalassemia:

Alpha (α) - Caused by defect in rate of synthesis of alpha chains. Beta (β) - Caused by defect in rate of synthesis in beta chains

Table 1 Hemoglobin Globin Chains: Variations in amino acid sequences give rise to different types of polypeptide chains. Each chain is designated by a Greek letter

Symbol	Name	Number of Amino Acids
α	Alpha	141
β	Beta	146
γ_A	Gamma A	146 (position 136: alanine)
γ_G	Gamma G	146 (position 136: glycine)
δ	Delta	146
ε	Epsilon	146
ζ	Zeta	141

Beta Thalassemia:

B-thalassemia is an autosomal recessive disorder more common in people of Mediterranean, Middle Eastern, or Asian descent. The underproduction of β globin chains is most frequently caused by point mutations with single nucleotide substitution or oligonucleotide addition or deletion.116 The β globin gene is on chromosome 11 [7]. The β-thalassemia's are genetic disorders of hemoglobin synthesis characterized by deficient (β+) or absent (β0) synthesis of the β-globin subunit of hemoglobin molecule. Most individuals with thalassemia inherit their disorder as a Mendelian recessive. Heterozygous individuals have mild anemia and microcytosis and are categorized as having thalassemia minor or trait, and homozygous individuals have severe anemia of varying degrees and are characterized as having homozygous β-thalassemia or thalassemia major or intermedia, as discussed in detail below. Much rarer is a dominantly inherited β-thalassemia in which disease occurs in heterozygous individuals because of synthesis of a highly unstable β-globin variant. Usually, the disturbance is only in β-globin synthesis, but rare deletional mutations may remove one or more of the other genes on chromosome 11, resulting in forms of the disease characterized as δβ-, γδβ-, or εγδβ-thalassemia [8,9,10].

β-thalassemia is divided into four categories based on clinical manifestations:

- β-thalassemia silent carrier (heterozygous state) with no hematologic abnormalities or clinical symptoms
- β-thalassemia minor/trait (heterozygous state) with mild hemolytic anemia, microcytic/ hypochromic RBCs, and no clinical symptoms
- β-thalassemia intermedia with mild to moderate hemolytic anemia, microcytic/ hypochromic RBCs, moderate clinical symptoms, and transfusion independence.
- β-thalassemia major (Cooley's anemia, homozygous or compound heterozygous state) with severe hemolytic anemia, microcytic/hypochromic RBCs, severe clinical symptoms, and transfusion dependence

Table 2 Classification of β-thalassemia

Phenotype	Alleles	Clinical description
Silent carrier state		The mildest form of beta thalassemia, Mainly Asymptomatic
Beta thalassemia minor	β+/β βo/β	Heterozygous disorder resulting in mild hypochromic, microcytic hemolytic anemia
Beta thalassemia intermedia	β^+/β^+ β^o/β^+	Severity lies between the minor and major
Beta thalassemia major	β^o/β^o	Homozygous disorder resulting in severe transfusion-dependent hemolytic anemia

Alpha-thalassemia

Is the type of thalassemia caused by decreased or absent production of α chain. α-thalassemia is usually caused by gene deletion. In α -thalassemia, the decreased production of a chains can manifest in utero because the α chain is a component of both fetal and adult hemoglobin. To inheritance of alpha thalassemia simultaneous or some genetic factors causing sustain production globin chains, (Hb F) in adults [11].

Hemoglobin H forms when only one normal alpha gene has been inherited. This causes significantly impaired alpha globin production. In the neonatal period, this will cause an excess of gamma, and in adults, this leaves an excess of beta-globin chains. Free alpha chains are insoluble. Both gamma and beta chains are soluble and make homotetramers. Hemoglobin H is made of four beta chains, and Hb Barts is made of four gamma chains. They are, however, unstable and some precipitate within the cell, leading to a variety of clinical manifestations. Hb H in adults can make up to 40% of circulating hemoglobin in affected individuals. This hemoglobin is more susceptible to oxidant injury and has poor oxygen-carrying capacity. Its affinity is ten times more than Hb A. It has an abnormal oxyhemoglobin dissociation curve. This means that it can bind to oxygen but does not deliver it to tissues normally [12].

Clinical syndromes of α-Thalassemia include:

- Silent carrier state (1 α gene deletion)
- Alpha-Thalassemia minor (2 α genes deletion)
- Hemoglobin H disease (3 α genes deletion)
- Hb Bart Hydrops Fetalis Syndrome (4 α genes deletion)

Table 3 Classification of Alpha-thalassemia

Phenotype	Genotype	Clinical description
Silent carrier state	- α/α α	- The effect on hemoglobin synthesis is

		minimal. No hematological abnormalities are present, and no clinical symptoms present.
Alpha Thalassemia minor	- -/α α or - α/- α	- A mild asymptomatic microcytic hypochromic hemolytic anemia. - -/α α (cis, heterozygous, αo/α, Asian) - α/- α (trans, homozygous, α+/α+ African).
Hemoglobin H disease	- -/- α	- A mild to moderate microcytic hypochromic hemolytic anemia, - The disease is noticed in childhood or in early adult life; anemia and hepatosplenomegaly are noted
Hb Bart / Hydrops Fetalis Syndrome	- -/- -	-A severe microcytic hypochromic hemolytic anemia. Incompatible with life. -Lethal: infants stillborn or die within hours of birth

Pathophysiology of thalassemia

Decreased or absent production of a particular globin chain that results in decreased amount of Hb, microcytosis, hypochromia, variable target cells (codocyte), ovalocytes, and basophilic stippling. Unequal production of the α- or β- globin chains which leads to: Imbalance in the α/β ratio. Decreased RBCs survival that is a significant contributor to anemia. Formation of unusual polypeptide combinations to make Hb In β-thalassemia, the unpaired, excess α chains precipitate in RBCs and damage their surfaces, which will be destructed by macrophages in the BM or circulation. The premature death of RBCs in the BM is called ineffective erythropoiesis, although the BM attempts to produce RBCs, but it can't release viable cells to the circulation or the cells that are released are destroyed in the spleen. In β-thalassemia, anemia is developed from ineffective erythropoiesis and increased destruction. β-thalassemia individuals are asymptomatic during fetal life and through approximately 6 months of age, because Hb F (α2γ2) is the predominant Hb and switching from γ to β chain didn't occur. Symptoms usually begin to appear between 6 and 24 months of age, after completion of the γ to β switch. The mechanism sees that α thalassemias results in decreased alpha-globin production, therefore fewer alpha-globin chains are produced, resulting in an excess of β chains in adults and excess γ chains in newborns. The excess β chains form unstable tetramers called hemoglobin H or Hb H of four beta chains. The excess γ chains form tetramers which are poor carriers of O2 since their affinity for O2 is too high, so it is not dissociated in the periphery. Homozygote α0 thalassemias, where numerous γ4 but no α-globin's occur at all (referred to as Hb Barts), often result in death soon after birth [13,14,15].

The signs and symptoms of thalassemia:

The signs and symptoms vary depending on the severity of the thalassemia, we can find all symptoms of anemias starting by Fatigue, Weakness, Irritability,

fussiness Fevers, Pale or yellowish skin, Dark urine. People affected by milder forms of thalassemia can develop mild anemia or may have no signs or symptoms of the condition at all. Intermediate forms of thalassemia can cause mild to moderate anemia and may be associated with other health problems such as slowed growth, delayed puberty, bone problems and/or an enlarged spleen. In addition to the signs and symptoms seen in intermediate thalassemia, people with severe forms of thalassemia may also experience severe anemia, poor appetite, paleness, dark urine, yellow discoloration of skin (jaundice), and enlarged liver or heart Hepatosplenomegaly are due to extramedullary hematopoiesis, Jaundice is results from the excessive destruction of RBCs and their precursors leading to an increase in the level of plasma bilirubin [16,17,18].

Complications of thalassemia:

The complications are vary depending on the severity of the thalassemia. In cases of severe thalassemia, the following complications can occur:

5.1 Iron overload: Iron accumulation in various organs is a serious complication in β -thalassemia major and is a significant cause of death in adults. People with thalassemia can get an overload of iron in their bodies, either from the disease itself or from frequent blood transfusions. Too much iron can result in damage to the heart, liver, and endocrine system, which includes glands that produce hormones that regulate processes throughout the body [19].

5.2 Bone deformities: Marked bone changes due to an expanded marrow cavity caused by extreme erythroid hyperplasia. Skull radiographs may demonstrate a typical “hair on end” appearance. Long bones may exhibit a lacy appearance from marrow expansion, which may predispose to pathological fractures. A typical face results with prominence of the forehead (frontal bossing). Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the risk of broken bone [20].

5.3 Enlarged spleen: Increased splenic function (sequestration or destruction of circulating cells) can lead to increase the size of spleen because the spleen is becoming working harder than normal. Splenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. Severe enlargement of the spleen may necessitate its removal [21].

5.4 Physical growth and development are delayed: anemia can cause the growth of a child to slow down. Puberty may also be delayed in children with thalassemia [22].

5.5 Heart problems: Both the anemia caused by thalassemia and the iron overload that is related to the disorder and its treatment can contribute to cardiac issues. Diseases, such as congestive heart failure and abnormal heart rhythms, may be associated with severe thalassemia [23].

5.6 Endocrine disorders: Endocrine disorder is from iron overload problems in patients with thalassemia. The anterior pituitary is very sensitive to iron deposition in tissues. This sensitivity can cause serious disturbances in the synthesis and secretion of hormones [24].

5.7 Infection: People with thalassemia have an increased risk of infection. Thalassemic patients receive long-term blood and blood products especially blood transfusion dependent and are at risk of viral infection such as viral hepatitis.

Despite hepatitis B vaccines for donors and thalassemic patients, the prevalence of these viral diseases among these patients is greatly reduced [25].

Laboratory Diagnosis of Thalassemia

The most important in the approach diagnosis of thalassemia need to start with patient's individual history, family history and ethnic background important. Perform physical examination. Pallor indicating anemia, Jaundice indicating hemolysis. Splenomegaly due to pooling of abnormal cells. Skeletal deformity, especially in beta thalassemia major. Most children with moderate to severe thalassemia receive a diagnosis by the time they are 2 years old. People with no symptoms may not realize they are carriers until they have a child with thalassemia.

Diagnosis of Thalassemia require a combination of laboratory tests including the measurement of red blood cell indices by automatic hematology analyzer, Hb analysis, and quantification of Hb A2 and Hb F. The high-performance liquid chromatography (HPLC) and capillary zone electrophoresis (CE) system can distinguish thalassemic diseases and the carriers. Also, DNA analysis, and various techniques have been used for point mutation detection. Moreover, thalassemia genotyping can be carried out by real-time polymerase chain reaction (PCR).[26].

Complete Blood Count (CBC)

The CBC can check hemoglobin levels and the level and size of red blood cells. The CBC is performed using basic laboratory equipment or an automated hematology analyzer, which counts cells and collects information on their size and structure [27]. CBC is often the first investigation in a suspected case of thalassemia. A CBC showing low hemoglobin and low MCV is the first indication of thalassemia, after ruling out iron deficiency as the cause of anemia [2,28]. Also, Reticulocyte count now becoming important part in CBC and can measures how fast reticulocytes, or immature red blood cells, are produced and released by the bone marrow (Asses the bone marrow activity).

Peripheral Blood Smear in Thalassemia

Staining of blood smear is also important to study the blood cells. Staining of blood smears allows a better look at the blood cells. Examination of the peripheral blood smear should be considered, along with review of the results of peripheral blood counts and red blood cell indices, an essential component of the initial evaluation of all patients with hematologic disorders. The examination of blood films stained with Wright's stain frequently provides important clues in the diagnosis of thalassemia [29,30]. Blood film: varies between the different types of thalassemias. Blood film in thalassemia showing microcytic, hypochromic RBCs; target cells often present. Basophilic stippling especially in Mediterraneans. Hb H inclusions (denatured β-globin chains, Golf ball) typically appear as small, multiple, irregularly shaped greenish blue bodies uniformly distributed throughout the RBC.

Table 4 Hematological profiles and Peripheral Blood Smear

Phenotype	CBC	Peripheral Blood Smear
Silent Carrier State for β Thalassemia	no hematologic abnormalities.	no hematologic abnormalities.
β- thalassemia trait	- Hb may be ↓ but is not usually <10.0g/dL. - RBCs count: normal or slightly - MCV ↓ 63–77fL - MCH ↓	- Blood film: microcytic, hypochromic - RBCs; target cells often present. - Basophilic stippling especially in Mediterranean's.
β-Thalassemia major	- Hb can fall as low 3 to 4 g/dL. - MCV (50 – 70 fL) and MCH are decreased. - Retics range from 2 – 8 %,	Blood film will show: - marked microcytic hypochromic RBCs - anisocytosis and poikilocytosis - target cell - basophilic stippling - many nucleated RBCs (NRBCs)
α-Silent Carrier State	- No hematologic abnormalities present. - May see borderline low MCV (78-80fL).	No hematologic abnormalities present.
α-Thalassemia minor	- Mild anemia with Hb ranges from 12 to 13 g/dL - Hb Bart ranges from 5-15 % at birth. - Hb H is not usually present. - Hb: 7-10 g/dL. - Retics: 5 – 10 %.	RBCs are microcytic hypochromic with marked poikilocytosis. Target cells. - Hb H inclusions (denatured β-globin chains, Golf ball) typically appear as small, multiple, irregularly shaped greenish blue bodies uniformly distributed throughout the RBC.
Hb Bart & Hydrops Fetalis Syndrome	- Hb and Hct are decreased - RBCs count is disproportionately high relative to the degree of anemia - MCV is very low and MCH is slightly decreased -RDW is elevated (anisocytosis)	Blood film: microcytic, hypochromic pattern, poikilocytosis, target cells, elliptocytes, basophilic stippling, polychromasia & NRBCs.

Hemoglobin Electrophoresis in Thalassemia

Hemoglobin electrophoresis is used in thalassemia to identify hemoglobin types include hemoglobin A1 (HbA1), hemoglobin A2 (HbA2), hemoglobin F (Hb F; fetal and other hemoglobin variants which me be combined with thalassemia. hemoglobin electrophoresis includes cellulose acetate electrophoresis, microcolumn chromatography, alkaline denaturation test, cation-exchange high performance liquid chromatography (HPLC) [31].

Table 5 Hemoglobin electrophoresis Profiles for Beta Thalassemia

Phenotype	A	F	A_2
Normal	97	≤ 1	2-3
Beta thalassemia minor	80 -90	1-5	3-7
Beta thalassemia intermedia	30-50	50-70	0-5
Beta thalassemia major	0-20	80-100	0-3

Table 6 Hemoglobin electrophoresis Profiles for Alpha Thalassemia

Phenotype	A	F	A_2
Normal	97-98 %	0	0
Silent Carrier	96-98%	1-2% (at birth)	0
Alpha Thalassemia minor	85 -95%	2-8% (at birth)	≤ 2
Hemoglobin H disease	Dec	≤ 10% (at birth)	5- 40%
Hb Bart / Hydrops Fetalis Syndrome	0	70-80% (with 20% Hb Portland)	0-20%

DNA analysis

DNA tests are used to help confirm mutations in the alpha and beta globin-producing genes. DNA testing is not routinely done but can be used to help diagnose thalassemia and to determine carrier status, if indicated. More than 250 mutations have been associated with beta thalassemia, though some cause no signs or symptoms [32]. For example, several studies have examined that MTHFR C677T, prothrombin G20210A (PT G20210A), and Factor V Leiden G1691A (FVL G1691A) polymorphism play a crucial role in the development of β-thalassemia major, the heterozygote genotype of FVL G1691A and PT G20210A and the frequencies of recurrent thromboembolism was double in β-thalassemia patients The heterozygous and homozygous genotypes of FVL was statistically significantly correlated with the high risk of thrombosis. [33,34]. MTHFR C667T and FV gene polymorphism altered the function of enzymes and increased the risk of thrombosis, pregnancy complications. [35,36].

Iron profile studies

Serum iron, ferritin, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), and percent saturation of transferrin) are also done to rule out iron deficiency anemia as the underlying cause [2,37].

To differentiate between β-thalassemia minor and IDA

- RBCs count is normal or slightly elevated in β-thalassemia minor, while it is decreased in IDA.
- RDW is more often normal in thalassemia trait than in IDA (↑).

- Serum iron and ferritin are decreased in IDA, while they are normal in β-thalassemia minor.
- HbA2 is elevated in β-thalassemia minor, while it is decreased in IDA.
- Target cell is prominent in β-thalassemia minor more than IDA

Prenatal Diagnosis

Prenatal diagnosis of Beta-thalassemia ideally is conducted in the first trimester of pregnancy using chorionic villus tissue for DNA analysis by PCR to detect point mutations or deletions. Later, second trimester fetal blood analysis is done to estimate relative rates of synthesis of globin chains of hemoglobin. This is performed to estimate relative rates of synthesis of globin in mid- trimester fetuses and base the diagnosis on the beta-to-alpha (b/a) biosynthetic ratio [4].

Newborn Screening and Definitive Diagnosis

Newborn screening for beta thalassemia disease is performed by high performance liquid chromatography (HPLC) testing to determine the presence or absence of hemoglobin (Hgb) in whole blood. Unaffected infants will have mostly fetal hemoglobin (Hgb F) and some adult hemoglobin (Hgb A). Genetic testing of amniotic fluid is useful in those rare instances where a fetus has an increased risk for thalassemia. This is particularly important if both parents likely carry a mutation because that increases the risk that their child may inherit a combination of abnormal genes, causing a more severe form of thalassemia. Prenatal diagnosis with chorionic villi sampling at 8 to 10 weeks or by amniocentesis at 14 to 20 weeks' gestation can be carried out in high-risk families [2].

COVID-19 Pandemic and Thalassemia:

Coronavirus disease (COVID-19) has quickly spread around the world, resulting in a worldwide high mortality and morbidity economic recession as well as a health problem in several countries and regions [38]. The unanticipated outbreak of the COVID-19 pandemic has shocked the world in terms of both lives and livelihood. SARSCoV-2 virus primarily affects the respiratory system, although other organ systems are also involved [39]. Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness Haemoglobinopathy itself is a chronic disease. Patients with hemoglobinopathy are a specific population with special health needs [40]. More patients with hemoglobinopathy (35.8%) had severe COVID-19 infection compared to the general population [41]. There are several reasons why people with thalassemia might be at risk for more severe outcomes with COVID-19. For example, some of the common complications and coexisting conditions caused by thalassemia may also worsen COVID-19 like Iron overload, Splenectomy, Hypercoagulability and Reduced immune response by Excess iron can build up in regions of the body such as the hypothalamus and adrenal glands [42]. The progression of COVID-19 infection in hemoglobinopathy patients in general and thalassemia in specific is not well recognized and still an area of debate and

under investigation. Thalassemia patients have higher risk of exposure to SARS-CoV-2 due to the frequent hospital visits for regular blood transfusions [43].

There are some challenges reported especially for patients with thalassemia major which they are depending on blood transfusion. Due to COVID-19 pandemic, many countries have adopted unprecedented lockdown to minimize the spread of transmission. Restriction of nationwide human mobility and fear of COVID-19 infection has put thalassemia patients in a life-threatening situation because of an acute shortage of blood supply. In A study conducted by Yesim Tuba they found that blood donation decreased significantly during the pandemic, it was observed in this study that the blood needs of patients with TM could be provided. The results of the SF level showed that the management of chelation therapy should be more meticulous [44-47].

Conclusion

Thalassemia is the most common, inherited, single-gene disorder in the world. Treatment of the inherited blood disorder thalassemia depends upon the level of severity. There are many challenges in the transfusion practice of patients with TM due to fluctuations in the COVID-19 pandemic we encourage all researchers to conducting more study and meta-analysis study among patients suffering from thalassemia during COVID-19 crisis especially during infection, developing complications of disease and post vaccination.

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