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Time-Homogeneous Markov Process for Low Birth Weight Progression under Treatment

Michael Fosu Ofori[1*], Stephen Boakye Twum[2] and Osborne A. Y. Jackson[3]

[1]Department of Mathematics and Statistics, Kumasi Technical University, Ghana.
[2]Faculty of Applied Sciences, Methodist University College, Accra, Ghana.
[3]Department of Mathematics, University for Development Studies, Navrongo, Ghana.

Authors' contributions

This work was carried out in collaboration among all authors. Author MFO conceived the idea, collected the data, formulated the model and the matrix, wrote all the equations, simulated the model, analyzed the results and wrote the draft report. Author SBT edited the first draft and made some suggestions to the findings. Author OAYJ proofread the final draft. All authors read and approved the final manuscript.

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ABSTRACT

Background: Low birth weight incidence is quite high in the sub region, which has a public health concern. The weight of a baby at birth has dire consequences on the child as an infant, in childhood and as an adult.
Methods: The aim of this study was to explore and examine the spread and gravity of incidence of low birth weight by using a multi-state model to understand low birth weight progression. This study utilised data by Ghana Statistical Service from Multiple Indicators Cluster Survey conducted in 2011 to monitor progress of children and women.
Results: The multi-state Markov model dealt into the low birth weight transitions and severity under three treatments where transition intensities, transition probabilities and the mean sojourn times were estimated which show that low birth weight children tend to spend less time in bad states than in good states.
Conclusion: Generally, the survival of a low birth weight child in future time decreases from state 1 to state 4, hence treatment must be applied on time.

**Corresponding author: E-mail: mikeoffos@yahoo.com, mikeoffos70@gmail.com;*

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1. INTRODUCTION

Low birth weight (LBW) Children particularly those born of very low birth weight (VLBW) or extremely low birth weight (ELBW) are associated with high risk for multiple problems. The eventual effect of VLBW and ELBW infants are higher risk for cerebral palsy, developmental delay, mental retardation, visual problems (including blindness), hearing impairment, chronic lung disease and sudden infant death syndrome. As a result of this, these children require meticulous attention to all facets of their care. The following are some of the care that these infants require at the various level of life:

1. Resuscitation 2. Respiratory care: the majority of ELBW will require intubation at birth (to assist in their cardiopulmonary adaptation to extra-uterine life) and assisted ventilation for a prolonged period. 3. Cardiovascular: Most VLBW and almost all ELBW infants will require an umbilical arterial catheter for blood sampling and blood pressure measurement. 4. Oxygen therapy. 5. Fluids: on the first day of life, these infants should receive restricted fluids.

Low birth weight is prevalent in developing countries especially those in the Sub-Saharan region due to the high levels of malnutrition and infectious diseases. A child's birth weight is an important indicator of the child's vulnerability to the risk of childhood illnesses and the chances of survival. Globally, more than 20 million infants are born with weight less than 2.5 kg. The second highest incidence of low birth weight infants is the Sub-Saharan Africa (SSA) the world over (16%), with South Central Asia being the highest at 27% [1,2]. The most recent evidence in Ghana shows that approximately 10% of all births are LBW [3]. The UN envisages a fall in low birth weight by at least one-third in the proportion of infants. This target is in fact, one of the seven major goals for the current decade of the "A World Fit for Children" programme of the United Nations [4].

Low birth weight prevalence in Ghana is not so different from what pertains in the sub region [5]. The rate has been hovering around 10% according to the various results contained in the Multiple Indicators Cluster Questionnaire Surveys (MICS) and the Demographic and Health Surveys (DHS) conducted over the years [6-9]. This includes only a few babies who are weighed at birth or described as being "very small" or "smaller than average" when born. The major challenge is that most babies born in Ghana are not weighed at birth since most mothers give birth at home and not at health facilities. For instance, about 79% of babies born in Ghana were not weighed according to the 1998 DHS report (page; 98). Again, in the 2003 DHS information on birth weight was known for only 28% babies in the five years preceding the survey and for the 2008 DHS, birth weight was reported for only 43% of births in the five years preceding the survey. The 2006 MICS report also indicates that, overall, nearly 2 in 5 babies are not weighed at birth and approximately 9% of infants are estimated to weigh less than 2.5 kg at birth. However, some research findings at various facilities across the country put the prevalence rate above 16% which is higher than the 15% global average threshold making it a public health concern as a country. Again, according to the WHO data published in April 2011 LBW deaths in Ghana reached 6,056 or 3.23% of total deaths in the country. Currently LBW is among the top 20 causes of deaths in Ghana [10].

In this paper, we examine the intensities of LBW infants as they transit from one state to another; we study their progression in life as they transit from LBW to normal weight into adulthood or from LBW through ELBW to under nutrition. Due to the numerous challenges and problems that are associated with LBW babies at the various stages of life (at birth, childhood and adulthood), there is the need to closely monitor their progression at least before they attain age 1 by giving them some treatment from day 1 (at birth) to the 6^{th} month where exclusive breastfeeding ends. But to identify and deal with such children among LBW individuals can only be manifested along the transition chain which demands thorough investigations.

One thing that is known for sure in medical studies is the state of a patient at the time of examination. The researcher may not know the exact time but only the time interval in which a transition took place. Hence, homogeneous Markov models that are interval censored are most appropriate for such data [11]. The basic building blocks of the Markov processes include the transition intensities, probabilities and the distribution functions connected with the times

[12]. For a continuous-time Markov model, transitions can occur at any level (real-valued) time instant. For a time-homogeneous Markov jump process, the holding time in state i are modelled using exponential distributions. The exponential distributions may be adequate for many real-life situations, for example time until death, and waiting time before moving to another state. However, the exponential distributions are memoryless continuous distributions, hence a limitation in the application of Markov processes. It is likely the case that LBW babies starting on vitamins and exclusive breastfeeding who respond well to treatment will continue to respond well contradicting the Markov presumption and memory less attribute [13].

Transition probabilities for continuous-time homogeneous models only depend on the difference between the two observation times. That is, for all $t \geq 0$ the probability of moving from state i to state j is given by:

$$p_{ij}(s,t) = P[X_t = j|F_t] = P(X_t = j|X_s = i)$$

$$= P(X_{t-s} = j|X_0 = i), \forall t \geq 0, t > s$$

This is the Markov property, where F_t is the natural Filtration of the stochastic process. $P[X_t = j|F_t]$, therefore, represents the probability that stochastic process X_t is in state j at time t given the history of the process up to time t. The Markov property implies that all the history of the process is contained in the state currently occupied, $X_s = i$. The transition probabilities of a continuous time homogeneous Markov process $X_t, t \geq 0$ is given by:

$$p_{ij}(t) = P(X_t = j|X_0 = i)$$

The equations obey the Chapman-Kolmogorov equations:

$$p_{ij}(t+j) = \sum_{k \in X} p_{ik}(s) p_{kj}(t) \forall s, t > 0 \qquad (1)$$

1.1 Objectives

The main objective of the study is to model low birth weight progression under treatment using a multi-state modelling. The specific objectives include the following;

i. To identify the state(s) of LBW where more attention needs to focus
ii. To estimate the transition intensities and probabilities of each state
iii. To determine the sojourn time of each state
iv. To identify best treatment methods for LBW babies

2. METHODS

We formulate the continuous-time homogeneous model by examining the transition probabilities over a small time interval Δt. In our present study $\Delta t = \frac{1}{2}$ month making it suitable to make assumption that transition rates are constant over these intervals. The transition rates, also referred to as forces of transition or transition intensities, are basic notion in continuous time Markov jump procedures [14-18]. Unlike probabilities transition intensities can take values above one. To be able to transform the transition probabilities by avoiding mathematically technical problems, we assume that the functions $p_{ij}(t)$ are continuously differentiable and are dependent on initial condition defined as:

$$p_{ij}(0) = \delta_{ij} = \begin{cases} 0 \; if \; i \neq j \\ 1 \; if \; i = j \end{cases} \qquad (2)$$

δ_{ij} represents a Kronecker delta, $p_{ii}(0) = 1$ implies that at $t = 0$ the system remains at its original state and $p_{ij}(0) = 0$ implies no change of state when no time passes. The transition rate from state i to j is given by:

$$\alpha_{ij} = \frac{d}{dt} p_{ij}(t)|_{t=0} = \lim_{\nabla t \to 0} \frac{p_{ij}(\Delta t) - \delta_{ij}}{\Delta t}$$

α_{ij}, for $i = 1, \ldots, 4$ and $j = 1, \ldots, 7$, does not change over a period of time and agrees with the constrains; $\sum_{j \in X} \alpha_{ij} = 0$ and $\alpha_{ii} = -\sum_{i \neq j} \alpha_{ij}$

The probabilities of transition are obtained by solving a system of differential equations (Kolmogorov's forward equation) with respect to the initial conditions defined in (2), once the transition intensities are determined. The Kolmogorov's forward equation is given by:

$$\frac{d}{dt} p_{ij}(t) = \sum_{\forall k} p_{ik}(t) \alpha_{kj \; \forall i,j} \qquad (3)$$

Where, k represents a state through which the system can pass as it transits from state i to state j. Time homogeneous models are fitted to data to examine how effective a treatment is by comparing the forward and the backward transitions [19-22]. Therefore, this takes us to developing models that pave way for bidirectional transitions.

Chart 1. The state model for LBW progression of individual on treatment

State 1	State 2	State 3	State 4	State 5	State 6	State 7
LBW $< 2.5kg$	LBW $< 1.5kg$	LBW $< 1.0kg$	Undergrowth Children	Death	Normal Weight	Adulthood

Note: State 1; $1.5 \leq LBW < 2.5$*, State 2;* $1.0 \leq LBW < 1.5$*, and State 3;* $LBW < 1.0$

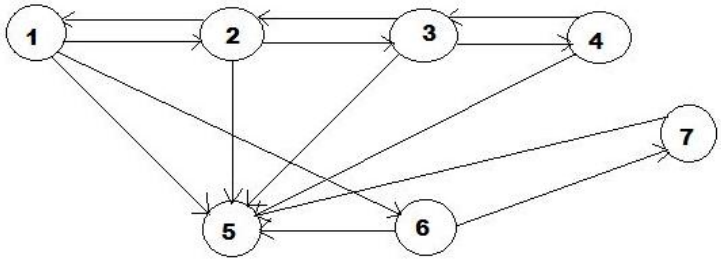

Fig. 1. The state model for LBW progression of individual on treatment

2.1 Formulation of Model

Given any point $t + \Delta t$, the state of low birth weight (LBW) baby is defined based on the gravity of LBW or whether the individual is undergrowth, dead, has gained normal weight or become an adult. Using these identified states, we define transition of LBW children on treatment by the state diagram in Fig. 1.

The arrows in the figure show all possible transitions among the seven states. From Fig. 1, it is clear that state 5 is an absorbing state, hence, there is no transition from this state. It is highly possible for a particular child to remain in the same state or move from that state into a lower state as the weight of that child deteriorates.

The model is developed based on the presumptions that between $(t, t + \Delta t)$, where Δt represents a minute value, there exists a movement from any one of the states $i = 1,2,\dots,4$ (transient states) to state $j = 1,2,\dots,7$ given as follows:

- The birth weight (LBW) of an individual child is anticipated to increase/improve owing to potency of treatment at a rate of α_{ij}, where $j = i - 1$
- Some of these children may not gain weight or not respond to treatment. These children can transit to state of lower (LBW) weight or can become undergrowth at a rate of α_{ij}, where $j = i + 1$
- From any state $i = 1,2,\dots,4$ an infected child can pass on (state 5) at a rate of α_{i5}
- A child in state $i = 1,2,\dots,4$ could also move to gain normal weight (state 6) at a rate α_{i6}
- A child in state 6 could also move into adulthood (state 7) at a rate of α_{i7}
- A child could continue to remain in the same state at a rate of

$$\alpha_{ii} = -\lambda_i = -(\alpha_{i,i-1} + \alpha_{i,i+1} + \alpha_{i5} + \alpha_{i6} + \alpha i7.$$

(The reason being that the sum of transition rates from any state sums up to zero).

The above assumptions are represented by the following transition rate matrix $Q(t)$:

$$Q(t) = \begin{pmatrix} -(\alpha_{12}+\alpha_{15}+\alpha_{16}) & \alpha_{12} & 0 & 0 & \alpha_{15} & \alpha_{16} & 0 \\ \alpha_{21} & -(\alpha_{21}+\alpha_{23}+\alpha_{25}) & \alpha_{23} & 0 & \alpha_{25} & 0 & 0 \\ 0 & \alpha_{32} & -(\alpha_{32}+\alpha_{34}+\alpha_{35}) & \alpha_{34} & \alpha_{35} & 0 & 0 \\ 0 & 0 & \alpha_{43} & -(\alpha_{43}+\alpha_{45}) & \alpha_{45} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha_{65} & -(\alpha_{65}+\alpha_{67}) & \alpha_{67} \\ 0 & 0 & 0 & 0 & \alpha_{75} & -(\alpha_{75}) & 0 \end{pmatrix}$$

Once the transition rate matrix has been obtained, the matrix of transition probabilities can be obtained using Kolmogorov's forward differential equations defined in (3). This yields the following differential equations for the Markov jump processes:

$$\frac{dp_{i1}(t)}{dt} = -(\alpha_{12} + \alpha_{15} + \alpha_{16})\, p_{i1}(t) + \alpha_{21} p_{i2}(t) \quad \text{for } i = 1, 2; \tag{4}$$

$$\frac{dp_{i2}(t)}{dt} = \alpha_{12} p_{i1}(t) - (\alpha_{21} + \alpha_{23} + \alpha_{25})\, p_{i2}(t) + \alpha_{32} p_{i3}(t) \quad \text{for } i = 1, 2, 3; \tag{5}$$

$$\frac{dp_{i3}(t)}{dt} = \alpha_{23} p_{i2}(t) - (\alpha_{32} + \alpha_{34} + \alpha_{35})\, p_{i3}(t) + \alpha_{43} p_{i4}(t) \quad \text{for } i = 2, 3, 4; \tag{6}$$

$$\frac{dp_{i4}(t)}{dt} = \alpha_{34} p_{i3}(t) - (\alpha_{43} + \alpha_{45})\, p_{i4}(t) \quad \text{for } i = 3, 4; \tag{7}$$

$$\frac{dp_{i5}(t)}{dt} = \sum_{k=1}^{6} p_{ik}(t)\alpha_{k5} \quad \text{for } i = 1, \ldots, 6; \tag{8}$$

$$\frac{dp_{i6}(t)}{dt} = \alpha_{16} p_{i1}(\mathrm{t}) - (\alpha_{65} + \alpha_{67})\, p_{i6}(\mathrm{t}) - (\alpha_{75})\, p_{i7}(\mathrm{t}) \quad \text{for } i = 1, 6, 7; \tag{9}$$

$$\frac{dp_{i7}(t)}{dt} = \alpha_{67} p_{i6}(\mathrm{t}) \quad \text{for } i = 6; \tag{10}$$

Equations (4) to (10) represent all the possible transition probabilities from i, for $i = 1,2 \ldots, 4$, to state $j = 1, \ldots, 7$. $pij\ (t)$ represents the probability that a child in state i makes a transition to state j and its coefficients represent the transition rates. For example, in equation (4), $-(\alpha_{12} + \alpha_{15} + \alpha_{16}) = \alpha_{11}$. These states denoted by i are defined based on the LBW severity groupings. This means there is a possibility of a forward or backward movement transition between transient states due to failure or efficacy of treatment respectively. There is no possible transition from state $i = 5$ because that state is an absorbing state. This state represents death of an infected individual.

3. RESULTS

3.1 Transition Intensities

From the estimated intensities, we see that LBW babies are almost ten times as likely to develop symptoms than die without symptoms (transition from state 1). After weight deterioration onset (state 2), VLBW, progression to severe state, ELBW (state 3) is about 63% more than recovery. Again, progression from ELBW (state 3) to under nutrition (sate 4) is also about 83% more than recovery. Once in severe state (under nutrition), death is more likely than recovery, and a mean of -1/-3.6=0.28 years or 3.3 months is spent in state 4 before death or recovery.

3.2 Transition Probability Matrix

From Table 3, a particular child (baby) in state 1, LBW, has a 0.64 probability of dying six months from now, a probability of 0.71 of dying as a VLBW (state 2) child and probabilities of 0.88 and 0.97 of dying as an ELBW child or under nutrition respectively. The same child in state 1 has about 1% chance of going into adulthood or a higher chance of gaining normal weight after treatment. In all the probability that a baby will be dead in six months' time increases through state 1 to state 4.

3.3 Forecast of the Total Length of Stay in Each State

We need to forecast the total time spent in the good states and the bad states by individual babies who are on treatment before death or going into adulthood from the study. Estimates of the forecasted total lengths of time spent in each state j between two future time points t_1 and t_2 are estimated using the formula:

$$L_j = \int_{t_1}^{t_2} P_{ij}(t)dt$$

Where i is the state at the start of the process, which defaults to 1. The results are shown in Table 4.

From the model, each baby is forecasted to spend approximately 1.56 months with LBW (state 1), 1.61 months with VLBW (state 2), 1.18 months ELBW (state 3) and 0.90 months with under nutrition (state 4). This means that a baby who transits into VLBW state spends more time in this state in recovery or otherwise than any other state in transition. The results further show that LBW babies on treatment are expected to spend more time in good states compared to the time spent in bad states.

3.4 Expected Holding Times (Mean Sojourn Times)

The expected holding time also known as the mean sojourn time in each state describes the average time an individual spends in each state in a single stay before he/she makes a transition to another state. The mean sojourn time in each

Table 2. Transition intensities and their corresponding confidence intervals for the model

(ij)	Intensities(α)	Confidence intervals
State 1 – state 1	-3.63610	(-1.594e+00, -6.130e-01)
State 1 – state 2	3.21970	(5.211e-01, 1.470e+00)
State 1 – state 5	0.00531	(6.659e-227, 5.101e+213)
State 1 – state 6	0.41680	(3.712e-02, 3.457e-01)
State 2 – state 1	1.24420	(1.303e-01, 8.780e-01)
State 2 – state 2	-3.52800	(-1.530e+00, -6.011e-01)
State 2 – state 3	2.15280	(3.491e-01, 9.810e-01)
State 2 – state 5	1.30490	(-1.506e+00, -5.368e-01)
State 3 – state 2	0.55100	(3.611e-02, 6.212e-01)
State 3 – state 3	-3.30760	(-1.506e+00, -5.368e-01)
State 3 – state 4	2.75650	(4.355e-01, 1.289e+00)
State 3 – state 5	0.03570	(1.951e-74, 1.443e+65)
State 4 – state 3	0.47460	(1.695e-02, 9.822e-01)
State 4 – state 4	-3.60820	(-1.689e+00, -5.695e-01)
State 4 – state 5	3.13360	(4.984e-01, 1.456e+00)
State 6 – state 5	0.01350	(6.808e-310, 4.328e+298)
State 6 – state 6	-1.36400	(-5.080e+00, -3.663e-01)
State 6 – state 7	1.36400	(3.663e-01, 5.080e+00)
State 7 – state 5	1.01400	(3.343e-01, 3.075e+00)
State 7 – state 7	-1.01400	(-3.075e+00, -3.343e-01)
$-2 \times LL$	318.6697	

Table 3. Transition probability matrix (probability that a baby would be dead 6 months from now)

States	State 1	State 2	State 3	State 4	State 5	State 6	State 7
State 1	0.04741	0.09031	0.10391	0.09997	0.64164	0.00537	0.01139
State 2	0.03491	0.06824	0.08574	0.08983	0.71046	0.00380	0.00702
State 3	0.01028	0.02194	0.03675	0.04863	0.87975	0.00103	0.00161
State 4	0.00170	0.00396	0.00837	0.01349	0.97210	0.00016	0.00022
State 5	0.00000	0.00000	0.00000	0.00000	1.00000	0.00000	0.00000
State 6	0.00000	0.00000	0.00000	0.00000	0.99192	0.00028	0.00780
State 7	0.00000	0.00000	0.00000	0.00000	0.99772	0.00000	0.00228

Table 4. Total length of stay (total time spent healthy or diseased, before death)

State1	State 2	State 3	State 4	State 5	State 6	State 7
1.5626209	1.6098687	1.1769251	0.8990542	Inf	0.1297565	0.1745963

state i for $i = 1,2,\ldots,4$, is estimated as $\frac{1}{\lambda_i}$, where $\lambda_i = \sum_{i \neq j} \alpha_{ij}$ is the total force of transition out of state i. For example, the expected holding time in state 1 is 1.0117087 as shown on Table 5. Results from Table 5 show estimates of the holding time, the standard error (SE), the lower bound (L) and the upper bound (U) for each of the transient state i.

From Table 5, if an individual is in state 3 (corresponding to ELBW) he spends more time in that state before making a transition to other states. This could be due to the time taken by an individual to respond to treatment since state 3 is the worst state in LBW progression.

3.5 The Jump Chain

This is when a Markov process is observed at the times it makes transitions to a new state. In other words, a jump chain is a stochastic matrix *R* of probabilities where each row sums up to one, on the state space X_t, which gives the conditional property of the next state an individual goes to after leaving state i. If $\alpha_{ii} > 0$ then given that there is a jump out resulting in having $R_{ii} = 0$ and if $\alpha_{ii} = 0$ then we never leave state i meaning that $R_{ii} = 1$ (state 5). The computed matrix probabilities of each state being next (also known as the jump chain), together with the mean sojourn times in each state, fully define a continuous-time Markov model. This is more intuitively meaningful description of a model than the transition intensity matrix.

The matrix for the probabilities that the next state after state i is state j is approximated as $p_{ij} = \frac{\alpha_{ij}}{\lambda_i}$, for each i and j such that $i \neq j$, α_{ij} is the force of transition from state i to j and α_{ii} is the total force of transition out of state i. For example, $p_{12} = \frac{\alpha_{12}}{\lambda_1} = \frac{3.2197}{3.2197+0.0053+0.4+168} = 0.8841$, as shown in the matrix below.

The results from Table 6 indicate that, $R_{i,\ i-1} < R_{i,\ i+1}$, this means that there is a higher probability in moving to a worse state compared to moving to a better state. This is very evident among children in state 3 with the probability of moving to state 2 (recovery) is 0.1648 which is lower comparing with probability of making a move to state 4. This indicates that treatment is not very effective at this state. The probability that the death state is next is very common among children who have very low birth weight and under nutrition. These probabilities increase with severity of LBW into malnutrition.

3.6 Ratio of Transition Intensities

We estimate ratio of two entries of transition intensity matrix at a given set of covariates values, together with a confidence interval estimated assuming normality on the log scale and using the delta method. For example, we may want to estimate the ratio of the progression rate α_{12} into the first state of LBW to the corresponding rate of α_{21}. The result is as shown on Table 6.

Table 5. Mean sojourn times (average period in a single stay in a state)

	Estimates	SE	L	U
State 1	1.0117087	0.2466322	0.6274099	1.631397
State 2	1.0427957	0.2484700	0.6537037	1.663480
State 3	1.1122332	0.2926396	0.6641043	1.862754
State 4	1.0195327	0.2827900	0.5919724	1.755904
State 6	0.7330605	0.4917397	0.1968570	2.729788
State 7	0.9863874	0.5583709	0.3252387	2.991527

Table 6. Probability of each State being next (R_{ij})

	To	1	2	3	4	5	6	7
From	1	0	0.8841	0	0	0.0015	0.1145	0
	2	0.2646	0	0.4572	0	0.2775	0	0
	3	0	0.1648	0	0.8245	0.0107	0	0
	4	0	0	0.1315	0	0.8685	0	0
	5	0	0	0	0	1	0	0
	6	0	0	0	0	0.0098	0	0.9902
	7	0	0	0	0	1	0	0

Table 7. Ratio of transition intensity matrix from state 2 to state 1

Estimate	SE	L	U
0.3865036	0.1694904	0.1636375	0.9129024

From the above it means that in our model, recovery from state 2 to state 1 is about 0.4 times as likely as progression.

3.7 The Percentage Prevalence of the Model

The percentage prevalence was plotted with a view to comparing the expected values and the observed values using the fitted time-homogeneous Markov model of which the results are displayed in Fig. 2. The results indicate that considering state $i = 1,2,\ldots,7$ the expected prevalence perfectly fit the observed data.

Treatment is applied right at state 1 and we see that the expected prevalence is below the observed prevalence, an indication that the treatment effect is positive. It declines from 100% at time zero to the sixth month. In state 2, the expected prevalence increases up to the first month at a rate of about 40% and declines to about 10% in the sixth month. In state 3, the prevalence rate increases from 0 to 20% in the second month and maintains the rate till the end of the period. This may be due to the fact that state 3 is a severe state and that recovery may be slow. State 4 also depicts a steady rise in the prevalence rate from zero to 18% to the end of time showing signs of poor recovery or no recovery. Within the absorbing state, the percentage prevalence for the death state increases sharply from 0 in the first month to about 60% in the sixth month. The percentage

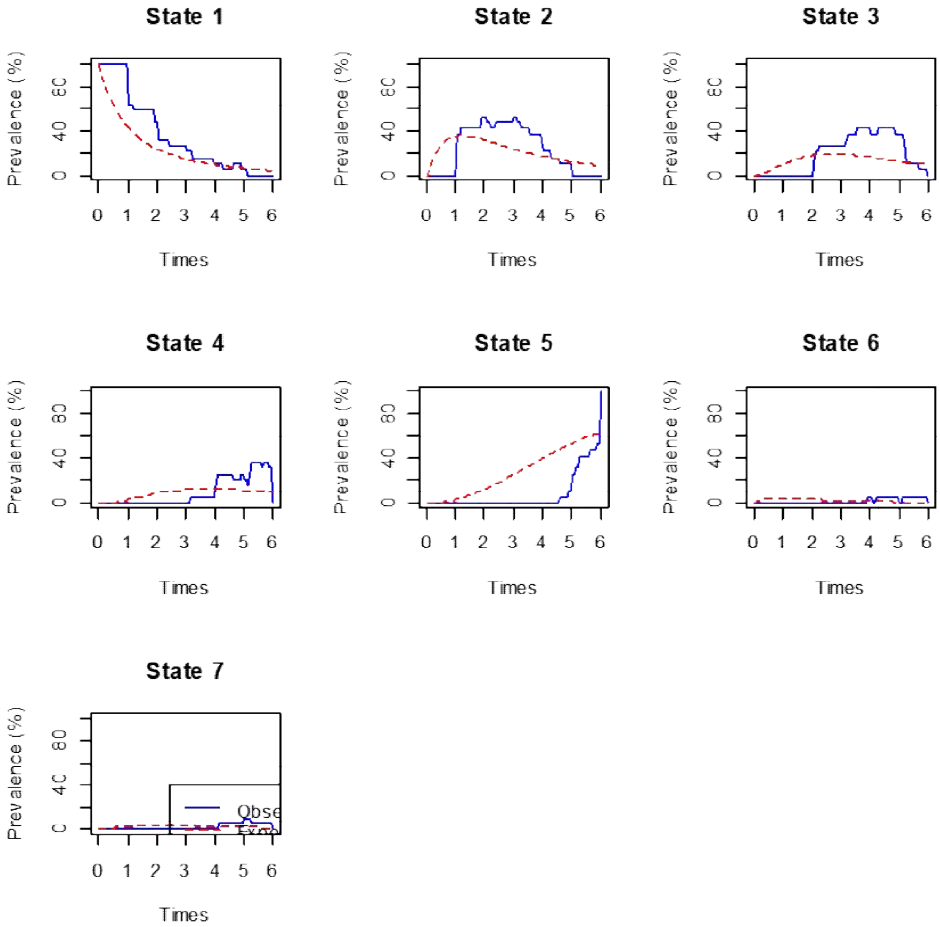

Fig. 2. Comparing observed and expected prevalence from the time-homogeneous model

prevalence of both the expected and the observed are perfectly fit for states 6 and 7 since both states represent normal weight gain and adulthood, respectively, and do not require treatment or have already transited from bad states.

4. DISCUSSION

The study investigates severity of LBW transition for LBW children put on treatment using a continuous-time homogeneous Markov model. Estimates that defined the parameters of LBW transition were computed which comprises transition intensities, expected holding times and probability of every state being next. The fitted model is employed in analysing the outcomes of the covariates on the transition intensities. The covariates were mothers' age, ANC and region of residence; and the treatments were, kangaroo mother care, exclusive breastfeeding and vitamins. The stochastic model was formulated based on the transition matrix as a result of the assumptions from the transition rates, from which the transition probabilities matrix was derived employing Kolmogorov's forward differential equations. Subsequently, simulations were made based on the state parameter values of the data, the transition matrix and the Kolmogorov's differential equations to obtain the required results.

The results from the estimated intensities show that LBW children are almost ten times more likely to develop symptoms than pass on without symptoms (transition from state 1). After weight deterioration sets in (state 2), transition to worst state (state 3) is about 63% above recuperation. Again, progression from (state 3) to under nutrition (sate 4) is also about 83% more than recovery. Once a baby transits through the various states and becomes malnourished, death is more likely than recovery with 3.3 months mean time spent in state 4 before death or recovery with its attendant cost.

A baby dying in future time was also estimated using probability intensity matrix. We realized that a baby in the first state, LBW, has from now a 0.64 probability of dying within the next six months, a 0.71 probability of being dead as VLBW child and probabilities of 0.88 and 0.97 of dying as ELBW (state 3) or under nutrition respectively. The same child under treatment in state 1 has just 1% chance of gaining normal weight or better chance of going into adulthood. In all the probability that a baby will be dead in six months' time increases through state 1 to state 4.

From our study, we needed to predict the full time spent in the bad states and the good states by individual babies put on therapy before passing on or going into adulthood. From the model, each baby is estimated to spend approximately 1.56 months with LBW (state 1), 1.61 months with VLBW (state 2), 1.18 months ELBW (state 3) and 0.90 months with under nutrition (state 4). This means that a baby who transits into VLBW state spends more time in this state before recovery or otherwise than any other state in transition.

The results further show that LBW babies put on therapy are supposed to spend more time in good states than the time spent in bad states. This corroborates the results of Shoko et al. [21] when they modelled HIV/AIDS transition put on variety of treatments in a cohort study in South Africa employing a time-homogeneous Markov procedure.

The expected holding time, which reports the mean time a particular child spends in each state in a single stay before transiting to different state was also analysed. The results indicate that if a child is in state 3 (representing ELBW) that child spends a lot of time in that state before transiting to different states. The reason might be the time required by the particular child to adhere to the therapy as state 3 is the severe state in LBW transition.

The jump chain analysis was also carried out (Table 6). The results show that the likelihood of moving to a severe state is higher than the likelihood of moving to a better state. This is highly evident by children in state 3 where the likelihood of moving to state 2 (recovery) is 0.1648 which is lower comparing with likelihood of moving to state 4. This indicates how ineffective treatment is in this state. The probability that the death state being next is very high for such babies with extreme low birth weight and under nutrition. These probabilities increase with severity of LBW into malnutrition.

The results further show that transition rates to LBW recovery are generally higher than the transition rate to severe LBW or LBW deterioration. However, the results show that the strongest predictor of LBW deterioration from state 1 to state 2 is attributable to the reaction to treatment.

5. CONCLUSION

In this paper, a continuous-time homogeneous Markov model is fitted to explore severity of LBW progression for LBW babies on treatment. Parameters that define progression of LBW were estimated and these include transition intensities, mean sojourn times and probability of each state being next or jumps. The fitted model is used to analyse the effects of the covariates on the transition intensities.

The results show that after weight deterioration onset (state 2) progression to severe state (state 3) is about 63% more than recovery. Again, progression from (state 3) to under nutrition (sate 4) is also about 83% more than recovery. This means that when babies weight deteriorates, treatment becomes ineffective hence they transit to bad states very fast. It is therefore necessary to initiate treatment as soon as LBW is detected. In all the probability that a baby will be dead in six months' time increases through state 1 to state 4.

The results further show that LBW babies on treatment are expected to spend more time in good states compared to the time spent in bad states. However, if their weights deteriorate and they transit to severe states (state 3), they spend more time in that state before making a transition to other states. This means that treatment for LBW babies must be applied at an early state (initial state) so that they can transit to recovery state rather than transiting to bad states.

Finally, the percentage prevalence was plotted to compare the expected values with the observed values using the fitted time-homogeneous Markov model. The results show that for the state $i = 1,2, \ldots ,7$ the expected prevalence fit the observed data perfectly well.

6. RECOMMENDATIONS

To prevent babies whose weight is low at birth, initiation of treatment must start at detection to avoid such babies transiting to worst states and possibly death.

Severe LBW babies (VLBW & ELBW) must be put under 24 hour intensive care and necessary treatment commence immediately.

ETHICAL APPROVAL

Ethical approval has been collected and preserved by the author(s).

AVAILABILITY OF DATA AND MATERIAL

Data available with Ghana Statistical Service.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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