

# Epidemioclinical Profile and Immediate Outcome of Low Birth Weight at the Reference Health Center in Commune VI of the District of Bamako, Mali

Mariam Maiga<sup>1</sup>, Oumar Coulibaly<sup>2</sup>\*, Mariam Traore<sup>1</sup>, Hibrahima Diallo<sup>1</sup>, Korotoumou W. Diallo<sup>3</sup>, Bourama Kane<sup>3</sup>, Alou Samake<sup>1</sup>, Mamadou Diallo<sup>1</sup>, Moussa Konate<sup>1</sup>, Mamadou Keita<sup>1</sup>, Mohamed Saydi Ag Med Elmehdi Elansari<sup>1</sup>, Diarra Sidy Moctar<sup>1</sup>, Mamadou Traore<sup>4</sup>, Djibril Kassogue<sup>5</sup>, Kadiatou Ba<sup>6</sup>, Pierre Togo<sup>2</sup>

<sup>1</sup>Pediatric Service of the Reference Health Center of the Commune VI, Bamako, Mali

<sup>2</sup>Pediatric Department of CHU Gabriel Touré, Bamako, Mali

<sup>3</sup>Mali Hospital, Bamako, Mali

<sup>4</sup>Pediatric Service of the Reference Health Center of the Commune V, Bamako, Mali

<sup>5</sup>Timbuktu Regional Hospital, Bamako, Mali

<sup>6</sup>Pediatric Service of the Reference Health Center of the Commune II, Bamako, Mali

Email: \*cheickcoul1@live.fr

How to cite this paper: Maiga, M., Coulibaly, O., Traore, M., Diallo, H., Diallo, K.W., Kane, B., Samake, A., Diallo, M., Konate, M., Keita, M., Elansari, M.S.A.M.E., Moctar, D.S., Traore, M., Kassogue, D., Ba, K. and Togo, P. (2023) Epidemioclinical Profile and Immediate Outcome of Low Birth Weight at the Reference Health Center in Commune VI of the District of Bamako, Mali. *Open Journal of Pediatrics*, **13**, 235-243.

https://doi.org/10.4236/ojped.2023.132029

**Received:** February 10, 2023 **Accepted:** March 18, 2023 **Published:** March 21, 2023

Copyright © 2023 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

http://creativecommons.org/licenses/by/4.0/

### Abstract

Introduction: Low birth weight is responsible for 9.1 million child deaths each year worldwide. It is the leading cause of perinatal and infant mortality. The objective of this work was to determine the epidemio-clinical profile as well as the future of low birth weight at the Reference Health Center of commune VI in the district of Bamako, Mali. Methods: Our study was descriptive and prospective over a year from April 1, 2018 to March 31, 2019. Data were taken from hospital records and newborn referral/evacuation forms. Data processing was performed using Epi Info software version 3.5.4 and Word. Results: The frequency of low birth weight was 34.94%. Multiparity accounted for 47.84%, sex ratio was 0.93, maternal arterial hypertension was present in 41.66%, genitourinary infection was in 58.37% and delivery was by low way in 86.12%. The majority of newborns had a gestational age between 28SA-33SA (56.52%) and a weight between 1501-1999 grams (47.36%). Mortality accounted for 18.66%. Conclusion: Low birth weight is common in our settings with modifiable risk factors. Practitioners must play on them to minimize its importance.

# Keywords

Low Birth Weight, Future, Risk Factors, Bamako, Mali

# **1. Introduction**

According to the World Health Organization (WHO), a low birth weight is strictly less than 2500 grams regardless of gestational age. More than 20 million babies in the world were born in 2015 with less than 2500 grams, or one in seven babies. Nearly three quarters of these babies were born in South Asia and sub-Saharan Africa. More than 80% of the 2.5 million newborns who die worldwide every year were underweight [1]. Several obstetrical factors have been implicated in the genesis of low birth weight and the impact on infant morbidity and mortality is recognized: young age of the mother, nutritional status before pregnancy, weight gain during pregnancy, parity, infectious and parasitic diseases, as well as the lifestyle and work of the mother during pregnancy are the determinants frequently reported in the literature (UNICEF WHO, 2004). In Mali, according to the report of the demographic and health survey (EDSM-VI) in 2018, 15% of newborns are considered to be low birth weight [2]. This prevalence varies from one region to another and is higher in rural areas (17%) than in urban areas (11%) [2]. In Bamako, a study carried out at the reference health center (C.S. Ref) in commune V found a prevalence of FPN of 12.66%, including 7.20% of FPN [3]. Low birth weight is an indicator of many public health problems. For example, children with low birth weight are at very high risk of sudden infant death syndrome, diabetes, cardiovascular disease, asthma, hearing problems and blindness. The chances of survival are closely associated with birth weight. Mortality is higher and physical health problems are increasingly common [4] [5]. Commune VI, an urban entity of Bamako, is not spared from this global scourge, which is the reason for this study.

The objective of this study was to determine the epidemioclinical profile and the immediate outcome of low birth weight at the Reference Health Center of commune VI in the district of Bamako, Mali.

# 2. Material and Methods

Our study was descriptive prospective and covered a period from April 1, 2018 to March 31, 2019 (*i.e.*, 12 months) at the Reference Health Center of commune VI in the district of Bamako, Mali. Newborns admitted during the study period with a birth weight of less than 2500 g were included, newborns with unusable medical records or with a birth weight of more than 2500 g were not included.

The data were encoded and analyzed using Epi Info software version 3.5.4 and Word. We considered that the difference was significant when p < 0.05 at the 95% threshold. When the conditions for using Pearson's chi-square wee not applicable, we used the Fisher exact test at the 95% threshold with significance when the Fisher exact < 0.05.

# 3. Results

During the period of our study, out of 598 newborns, 209 had low birth weight, which represents 34.94% of cases. The mothers were housewives (56.45%) and

they were married (82.79%). The average age of the mothers was 25.13 years with extremes of [15 years - 44 years]. They were not educated in 44.49%. They are mostly multiparous (47.84%). In a third of cases we note the total absence of CPN (10.52%) or less than 4 CPN (18.18%). Arterial hypertension was the most common medical history (41.66%), followed by diabetes (20.83%). During pregnancy, genitourinary infection was the most common (58.37%). In our study, the majority of newborns were In Born (59.33%), vaginal delivery predominated (86.12%) with a sex ratio of 0.93. They had a gestational age of 28 SA-33 SA with an average of 32.5 SA, the average weight was 1897 g with extremes [703 g - 2490 g], hypothermia in 65.07% and the age at admission was D0 (78.94%) (**Table 1**).

	Frequency (r	n = 209)	Percentage (%
	<18	19	9.09
Matana	18 - 30	146	69.85
Maternal age	31 - 40	37	17.70
	>40	7	3.34
	Unschooled	93	44.49
	Primary	49	23.44
Study level	Secondary	45	21.53
	Superior	16	7.65
	Koranic school	6	2.87
	Official	19	9.09
	Pupil/student	30	14.35
Mothers' profession	Saleswoman	42	20.09
	Housewife	118	56.45
Marital status	Bride	154	82.79
Maritai status	Unmarried	55	26.31
	Primiparous	62	29.66
Parity	Pauciparous	47	22.48
	Multiparous	100	47.84
	0	22	10.52
ANC	>4	149	71.29
	<4	38	18.18
	0	79	37.79
Number of ultrasounds	1 - 3	121	57.89
	>3	9	4.30

Table 1. Distribution of maternal and newborn characteristics.

Hypertension		20	41.66
Diabetes		10	20.83
HIV		6	12.50
Caesarean section		9	18.75
Appendectomy		2	4.16
Sickle cell disease		1	2.08
Malaria	Yes	17	8.13
	No	192	90.86
Genitourinary infection	Yes	122	58.37
	No	87	41.62
Mode of delivery	Low	180	86.12
	High	29	13.87
<b>6</b>	Male	101	48.32
Sex	Feminine	108	51.67
Unique		166	89.24
Twins		17	9.13
Triplet		3	1.61
<28 SA		5	3.62
28 SA - 33 SA		78	56.52
33 SA + 1J - 36 SA + 6J		55	39.85
≥37 SA		71	33.97
<1000		15	7.17
1001 - 1500		43	20.57
1501 - 1999		99	47.36
2000 - 2499		52	24.88
СР	26 - 30	56	26.79
Cr	31 - 33	153	73.20
Size	<47	151	72.24
Size	≥47	58	27.75
Heal		166	79.43
Death		39	18.66
xit against medical advice		4	1.91

The average length of hospitalization was 4.6 days with extremes [0 - 20]. The lethality during hospitalization was 18.66%. The presumed cause of death of newborns was dominated by infection (51.28%). They had a gestational age between 28SA-33SA (38.46%) [Fischer's exact test = 0.32; p-value = 0.07] and deaths occurred during the first 5 days of hospitalization (84.66%) [Fischer test = 0.05; p-value = 0.37]. The majority of newborns weighing less than 2000g were transferred to the Kangaroo Mother Care Unit (S.M.K), *i.e.*, 85.35% with an average weight of 1266 g. During the follow-up at SMK, we recorded a lethality of 4.47% and a dropout rate of 25.37%. Psychomotor development was considered good in 96.80% at 12 months.

## 4. Discussions

During the period of our study, of the 598 newborns, 209 had low birth weight, which represents 34.94% of cases. This is high compared to the national rate according to Mali's latest Demographic and Health Survey (EDSM-VI 2018) which reported a rate of 15% [2]. The high frequencies in developing countries seem to be explained by the multiplicity of risk factors, in particular malnutrition, insufficient monitoring of pregnancy, malaria and repeated urogenital infections during pregnancy [6]. Our rate is high compared to TELLY's. N et al. in Douentza which had recovered 9.2% [7]. Mombo-Ngoma G. et al. in 2016, in a multicentre study to assess whether young adolescent girls are at high risk for adverse pregnancy outcomes in sub-Saharan Africa between September 2009 and December 2013 in Benin, Gabon, Mozambique and in Tanzania found an overall prevalence of 10%. It should be noted that lower rates were found by Beddek F in Algeria, *i.e.* 6.4% (Beddek F and Demmouche A, 2014) [8], by Prosper Kakudji Luhete1, in the DRC, *i.e.* 6.4% (Luhete K, *et al.*, 2015) [6]. The disparity in LBW prevalence rates between areas could be explained by the place of study and the study population. Some populations may have lower than average birth weights due to genetic differences (OECD, 2015) [9].

We found a slight female predominance with a sex ratio of 0.93. This finding is contrary to that of Celstin. Mr. B (in Congo) [10] who had regained a slight male predominance (51.3%). However, according to Letaief *et al.* [11], on the one hand, and Bwana KI *et al.* [12], Lawoyin TO *et al.* [13], Onesmus Maina Muchemi *et al.* [14], Bazyar J *et al.* [15], Fu-Ying Tian *et al.* [16] on the other hand, female sex was associated with low birth weight. However, they offered no explanation for this association.

The average age of the mothers in our series was 25.13 years with extremes of [15 - 44 years]. In the SAASITA study in CONGO [17], newborns born to mothers aged 18 and under and 35 and over had a risk of low birth weight multiplied by 2.2 and 1.6, respectively. These results are in agreement with those of several other authors [12] and of a few studies showing that in relation to maternal age, young maternal age below 18 years is commonly associated with IUGR [18]. Indeed, adolescents who have not yet completed their own growth are more likely

to give birth to children with low birth weight [19]. Competition for nutrients between the growing adolescent and the fetus appears to be at the root [20]. In addition, the competition between pregnancy and growth has a particularly adverse effect on the micronutrient status of adolescents [20].

The majority of mothers were married in our study (82.79%). Danfakha F *et al.* in Mali did not find a statistically significant relationship between the marital status of mothers and the LBW (OR = 2.26 and CI: [0.88; 6.45]) [21]. Elsewhere in a study conducted in the gyneco-obstetrics department of the University Hospital of Antananarivo (CHUA), single status was significantly associated with low birth weight (p < 0.02) (Rakotozanany L.E *et al.* 2004) [22].

We found a predominance of multiparas in almost half (47.84%). Danfakha F in Mali had found a statistically significant association between TPNW and parity (OR = 2.67 and CI: 1.34; 5.29]) [21]. This result is similar to that of a study conducted in the health district of Barsalogho in the center north of Burkina Faso by Kaboré Patrick *et al.* who found that primiparity was a factor associated with very low birth weight (OR = 2.4 and CI: [1.4; 4.0]) (Kaboré Patrick *et al.* 2003) [23]. Elsewhere, other authors have found these same factors in their studies (OR = 1.73 and CI: [1.48; 2.01]) (Letaief M *et al.* 2001) [11] and (OR = 2.29 and CI: [1.54; 3.41]) (Rakotozanany L *et al.* 2004) [22]. The risk in multiparas could be explained by the fact that women in sub-Saharan Africa spend the majority of their lifespan, *i.e.*, 35 to 50% of the reproductive years, meeting the obligations of pregnancy, childbirth and breastfeeding [WHO/AFRO 2001]. However, in a study carried out by Fatima Beddek *et al.* in a hospital specializing in gynecology and obstetrics in Sidi Bel Abbes (western Algeria), low birth weight was not associated with parity (p = 0.4467) [8].

In our cohort, approximately 30% of mothers performed no ANC or less than three. DANFAKHA *et al.* found that pregnant women who had not attended the ANC service (less than 3 ANC) were more likely to give birth to newborns with NLW [21]. This finding is consistent with that reported by other researchers (OR = 1.46 [1.17; 1.83]) (Letaief M *et al.* 2001) and (OR = 3.19 and CI: [2.02; 4.96]) (Rakotozanany L *et al.* 2004) [11] [22]. It could be explained by the fact that the lack of follow-up of pregnancy does not make it possible to act on the curable medical causes of low birth weight or to monitor the results of systematic preventive measures against malaria, anemia or nutritional deficiencies. Unlike our study Samira Hassoune *et al.* found in their study on maternal factors associated with low birth weight that the number of antenatal consultations was not associated with LBW (OR = 1.6 and CI: [0.54; 4.70]) [24].

Genitourinary infection was mentioned in more than half of the women (58.37%) in our study. This result is inconsistent with that of Setondji [25] who had not established a correlation (p = 0.42) between infection during pregnancy and the birth of a child with low birth weight, Celestin [10] found that infection during pregnancy increased the risk (OR = 3.963; 95% CI: 2.716 - 5.784) of delivering a low-birth-weight newborn (p < 0.001). It corroborates the observations

made by other authors on this subject. Hassoune *et al.* during their study of maternal factors associated with low birth weight in Morocco, reported that infection was associated with low birth weight (p = 0.047) [24]. Infections that occur in pregnant women would disrupt the normal course of pregnancy. These disturbances can come from two elements. On the one hand the inflammatory reaction that accompanies any infection and on the other hand, the fact that during an infection the woman herself is weakened and forced to draw on her own energy and nutritional reserves [25]. Some infections, such as placental malaria, even affect the structure of the placenta and disrupt mother-child exchange. There are also all the intrauterine infections responsible for TORCH syndrome which disrupt the normal development of the fetus. These are toxoplasmosis, rubella, cytomegalovirus infection, herpes simplex and other infections such as HIV, syphilis, chicken pox etc.

In our series, hypertension was the most common medical ATCD (41.66%). Both in the univariate analysis (OR = 2.64, 95% CI: 1.41 - 4.88, p < 0.001) and in the multivariate analysis (OR = 3.313, 95% CI: 1.698 - 6.464; p < 0.000), the study by Celestin et al. [10] corroborates that conducted in Brazzaville by Mabiala-Babela et al., who found that high blood pressure during pregnancy was a factor increasing the risk of delivering a low-birth-weight newborn (p = 0.001)[26]. They had been joined by E. Nkwabong et al. (OR 2.4: 1.1 - 5.1) [27]. High blood pressure would disrupt blood circulation and therefore placental exchanges and would thus be the basis of the decrease in both oxygen and micronutrient intake. The FPN contributes to 60% to 80% of all neonatal deaths according to the WHO (WHO 2017) [28] and this same trend was observed in our study with 39 deaths recorded in our study of which 25% or 64.11% were from FPN. Allenson et al. 2016 [29], also found that 29.2% of early neonatal deaths in South Africa are of low birth weight and are associated with respiratory distress while 31.6% of early neonatal deaths in the UK are of low birth weight [30], among them (27.3%) are associated with complications of the placenta, cord and membranes [29]. In our cohort, infection was the presumed cause of death (51.28%) followed by respiratory distress (23.07%) and perinatal anoxia (20.51%).

The early neonatal deaths recorded following complications (birth infection, respiratory distress and perinatal anoxia) during our study could be explained by the lack of adequate resuscitation equipment and unsuitable maternity premises as well as insufficient prenatal consultations.

# **5.** Conclusion

Low birth weight is common in our communities with modifiable risk factors. Practitioners must play on them to minimize its importance.

#### **Conflicts of Interest**

The authors declare no conflicts of interest regarding the publication of this paper.

# References

- [1] WHO (2019) Newborns with Low Birth Weight in Canada, 2000 to 2013. C.S.R.S (Canadian Security Intelligence Service).
- [2] Mali Ministry of Health: 6th Phase Demographic and Health Survey (EDSVI), 81. http://www.DHSprogram.com
- [3] Tamboura, B. (2014) Study of Low Birth Weights at the Reference Health Center of Commune V in the District of Bamako from April to September 2013. Medicine Thesis. <u>http://www.keneya.net/</u>
- [4] Health Surveillance, Alberta Health and the Neonatal Research Unit, University of Calgary (1999) Maternal Risk Factors in Relationship to Birth Outcome. Accessed June 12, 2013.
- [5] Teshome, D., Telahun, T., Solomon, D. and Abdulhamid, I. (2006) A Study on Birth Weight in a Teaching Referral Hospital, Gondar, Ethiopia. *The Central African Journal of Medicine*, **52**, 8-11.
- [6] Luhete, P.K., Mukuku, O. and Kayamba, P.K.M. (2015) Study of Low Birth Weight Associated with Maternal Age and Parity in a Mother-Child Couple Population followed in Lubumbashi. *The Pan African Medical Journal*, 20, Article 246.
- [7] Telly, N., *et al.* (2020) Early Neonatal Complications of Low Birth Weight in Douentza, Mopti Region. *Malian Journal of Science and Technology*, 1.
- [8] Beddek, F. and Demmouche, A. (2014) Factors Related to Low Birth Weight in EHS in Obstetrics Gynecology in Sidi Bel Abbes (Western Algeria). *Pan African Medical Journal*, 16, Article 72. <u>https://doi.org/10.11604/pamj.2013.16.72.3127</u>
- [9] OECD (2015) Health at a Glance 2015: The OECD Indicators—8115072e. <u>https://www.oecd.org/unitedkingdom/Health-at-Glance-2015-London-Event-How-the-UK-Compares.pdf</u>
- [10] Mamba, T.C., *et al.* (2021) Factors Associated with Low Birth Weight of Term Newborns in Bukavu, Democratic Republic of Congo. *International Journal of Innovation and Scientific Research*, **53**, 123-131.
- [11] Letaief, M., Soltani, M.S., Salem, K.B. and Bchir, M.A. (2001) Epidemiology of Low Birth Weight in the Tunisian Sahel. *Public Health*, 13, 359-366. <u>https://doi.org/10.3917/spub.014.0359</u>
- [12] Bwana, K.I., Kilolo, N.U.E., Kabamba, N.M. and Kalenga, M.K.P. (2014) Risk Factors for Low Birth Weight in Semi-Rural Kamina, Democratic Republic of Congo. *The Pan African Medical Journal*, 17, Article 220.
- [13] Lawoyin, T.O. and Oyediran, A.B. (1992) A Prospective Study on Some Factors Which Influence the Delivery of Low-Birth-Weight Babies in a Developing Country. *African Journal of Medicine and Medical Sciences*, 21, 33-39.
- [14] Muchemi, O.M. Echoka, E. and Makokha, A. (2015) Factors Associated with Low Birth Weight among Neonates Born at Olkalou District Hospital, Central Region, Kenya. *Pan African Medical Journal*, **20**, Article 108. <u>https://doi.org/10.11604/pamj.2015.20.108.4831</u>
- [15] Bazyar, J., Daliri, S., Sayehmiri, K., Karimi, A. and Delpisheh, A. (2015) Assessing the Relationship between Maternal and Neonatal Factors and Low Birth Weight in Iran: A Systematic Review and Meta-Analysis. *Journal of Medicine and Life*, 8, 23-31.
- Tian, F.Y., Wang, X.M., Xie, C., Zhao, B., Niu, Z., Fan, L., Hivert, M.-F. and Chen, W.-Q. (2018) Placental Surface Area Mediates the Association between FGFR2 Methylation in Placenta and Full-Term Low Birth Weight in Girls. *Clinical Epigenetics*, 10, Article No. 39. https://doi.org/10.1186/s13148-018-0472-5

- [17] Kahindo, A.S., *et al.* (2022) Epidemiological Profile and Risk Factors for Low Birth Weight at the Katwa General Reference Hospital in North-Eastern DR Congo. *Ki-sangani Medical*, **12**, 578-583.
- [18] Mukuku, O., Mutombo, A.M., Kamona, L.K., Lubala, T.K., Mawaw, P.M., Aloni, M.N., Wembonyama, S.O. and Scholarm, O.N. (2018) Development of the Predictive Score for Acute Malnutrition in Children under 5. *The Pan African Medical Journal*, 29, Article 185. <u>https://doi.org/10.11604/pamj.2018.29.185.13713</u>
- [19] Faye, P.M., Diagne-Guèye, N.R., Paraiso, I.L., Bá, A., Guèye, M., Dieng, Y.J., Thiongane, A., Basse, I., Ndiaye-Diawara, N., Fall, A.L., Drame, M., Sy-Signaté, H. and Sarr, M. (2016) Postnatal Weight Growth among Low Birth Weight Newborns in the Neonatology Department of the Albert Royer National Children Hospital Center (ARNCHC) of Dakar: Incidence of Extrauterine Growth Retardation. *Journal de Pédiatrie et de Puériculture*, **29**, 20-27. https://doi.org/10.1016/j.jpp.2015.11.002
- [20] Diadie, H.O., Souley, R.A. and Balla, A. (2019) Nutritional Status of Pregnant Women and Impact on the Birth Weight of Newborns: Case of CSI Madina—Niamey. *Journal of Applied Biosciences*, 137, 13997-14006. https://doi.org/10.4314/jab.v137i1.7
- [21] Danfakha, F., et al. (2019) Factors Associated with very Low Birth Weight in a Reference Health Center in Bamako, Mali. Malian Journal of Science and Technology, No. 22.
- [22] Rakotozanany, L.E., *et al.* (2003) Factors Relating to Low Birth Weight at the CHUA Gynecology and Obstetrics of Befelatanana. *DESSP Memory*, 18-19.
- [23] Kabore, P., et al. (2007) Obstetric Risk Factors for Low Birth Weight at Term in Rural Sahelian Areas. Public Health, 19, 489-497.
- [24] Hassoune, S., *et al.* (2015) Maternal Factors Associated with Low Birth Weight: Case-Control Study in a Moroccan Public Hospital. *Pan African Medical Journal*, 20, Article 303.
- [25] Setondji, G.R.P. (2014) Low Birth Weight, Prematurity and Intrauterine Growth Retardation: Risk Factors and Consequences on Growth from Birth to 18 Months of Life in Beninese Newborns. Public Health and Epidemiology, Pierre and Marie Curie University-Paris VI, Paris.
- [26] Mabiala-Babela, J.R., Matingou, V.C. and Senga, P. (2007) Risk Factors for Low Birth Weight in Brazzaville, Congo. *Journal of Obstetrics Gynecology and Reproductive Biology*, **36**, 795-798. <u>https://doi.org/10.1016/j.jgyn.2007.06.007</u>
- [27] Nkwabong, E., Nounemi, N.K., Sando, Z., Mbu, R.E. and Mbede, J. (2015) Risk Factors and Placental Histopathological Findings of Term Born Low Birth Weight Neonates. *Placenta*, **36**, 138-141. <u>https://doi.org/10.1016/j.placenta.2014.12.005</u>
- [28] WHO (2017) Care of the Preterm and/or Low Birth Weight Newborn. WHO. http://www.who.int/maternal\_child\_adolescent/topics/newborn/care\_of\_preterm/en/
- [29] Allanson, E.R., et al. (2016) The WHO Application of ICD-10 to Deaths during the Perinatal Period (ICD-PM): Results from Pilot Database Testing in South Africa and United Kingdom. BJOG, 123, 2019-2028. https://doi.org/10.1111/1471-0528.14244
- [30] Ahankari, A., et al. (2017) Factors Associated with Preterm Delivery and Low Birth Weight: A Study from Rural Maharashtra, India. F1000Research, 6, Article No. 72. <u>https://doi.org/10.12688/f1000research.10659.1</u>