Problems in comprehension of informed consent in rural and peri-urban Mali, West Africa

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Background Clinical trials undertaken by industrialized nations in undeveloped nations pose several critical ethical dilemmas. One key potential problem concerns misunderstandings of the consent process by participants. Though other reports have begun to explore this area, needs remain to identify specific areas of misunderstanding.

Purpose To identify deficits in comprehension during consent processes in Mali, West Africa.

Methods After obtaining informed consent for participation for a malaria vaccine trial being conducted in two West African villages, we administered to participants a nine-item questionnaire testing their understanding of information relevant for their consent. After testing their ability to understand a multiple choice format, 78 of 100 subjects were administered the questionnaire in one village and 85 of 100 in the other.

Results Participants had difficulty comprehending several concepts relevant to informed consent: 90% of respondents did not understand withdrawal criterion, 93% did not understand the existence of study side effects, and 74% did not understand that they were enrolled in an investigation as opposed to receiving therapy. The response rate and percentage of correct answers was generally much higher in the village nearer an urban center than the more rural village. The percent of correct answers exceeded 50% for five questions in the urban village and for only two question in the more rural setting.

Limitations Potential limitations of this study are relating to translation, cultural differences in the notion of informed consent, staff differences between each village, the proportion who could not understand the survey instrument and the fact that the study explored participants' understanding of the consent process but did not observe the process itself.

Conclusions This study illustrates potential areas of miscomprehension in the consent process in a developing country. The degree of miscomprehension found in this study appeared to be more than that found in similar studies conducted in industrialized nations. Despite efforts to obtain truly informed consent, several factors make it more challenging in the developing world. This research highlights the need for more comprehensive studies of consent in developing countries. Such studies may eventually aid investigators in identifying, targeting and addressing specific areas of miscomprehension and thereby improve the informed consent process in the developing world. *Clinical Trials* 2006; **3**: 306–313. www.SCTjournal.com

Background

Clinical trials in the developing world sponsored by industrialized countries raise numerous practical and ethical difficulties. One critical challenge in such trials is the comprehension of the informed consent process by participants. While any clinical trial will involve some degree of miscomprehension with participants, where exactly, and to what degree do these deficits exist [1,2]?

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Prior studies

Several studies conducted in both Europe and the United States have assessed the degree of understanding of the informed consent process, and have illustrated flaws in comprehension [3]. Among consenting parents with children entering clinical trials in nine European countries, the notion of voluntary withdrawal was particularly misunderstood, with 20.7% of the parents miscomprehending the concept [4]. In a clinical trial of a surgical procedure, 33% of participants did not know they could withdraw at any time [5]. In a study of experimental chemotherapeutic agents for cancer, 48% of enrolled participants did not understand that the investigation was of a "non-standard treatment," [6] and 38% did not understand the potential for risks or side effects from the experimental chemotherapy. A qualitative study in East Africa confirmed many of these pitfalls in consent comprehension – specifically, understanding of risk, research versus treatment and autonomy. Interviews with consenting individuals revealed common themes such as, "It is inappropriate to question a doctor", and "there are no risks to this study ... people at the hospital have no bad intentions" [7]. While miscomprehension of consent is expected to some degree, these studies show particular areas predisposed to misunderstanding. Yet questions remain concerning the presence and degree of miscomprehension of studies in developing countries. With increasing research conducted in developing nations, and vast cultural barriers between participant and investigator, these questions are crucial. Though little data exist on this topic, research in the developing world, like that elsewhere, is predicated ethically on proper informed consent.

We examined the consent process for a malaria vaccine trial protocol in two villages in Mali, West Africa. This trial was a preliminary survey studying the incidence of both malaria and anemia for cohorts randomized to either chloroquine or placebo groups, along with minimal-risk weekly medical screening of child subjects (aged six months to five years). The trial's endpoints were malaria and anemia incidence with versus without chloroquine regimens over the course of one malaria season, to be later compared with use of malaria vaccine. The consent process for the malaria trial, which our team observed, was an oral consent administered by a PI to groups of two to four participants (ie, consenting parents) at a time. It lasted for approximately 40 minutes. Periodic breaks were taken to summarize and allow for questions as well as allotted time at the end for questions. Consent was given by thumbprint. All aspects of the consent tested in our study were explained at least twice to participants during this group consent process. The process was interactive to the extent that participants did regularly ask questions during the process. The exact nature and number of these questions was not quantified as the observer (MK) does not speak native Bambara.

Methods

Questionnaire development and administration

This study was approved by the Malian IRB/Ethics Committee as well as discussed with the IRB from the sponsoring host country's institution in July 2001. The questionnaire (Appendix) contains nine questions that test details about the vaccine study's consent. Each question is intended to probe a specific area in the consent process and has one correct answer, based on the vaccine study as explained during the consent process. These areas are summarized in Table 1. The questionnaire was developed in concert with the Malian IRB, who deemed the questions relevant and appropriate, over two sessions. We focused on assessing understandings of material presented in the consent process. It was hoped that relevant areas of comprehension could be examined. We based the questionnaire on observations of a few sessions of the informed consent process, and intensive discussions with both prominent village leaders and investigators. The questionnaire was translated from English to French by an experienced translator, and back-translated from French to English by a separate translator to ensure translational accuracy. The test administrator who orally delivered the test in each village was responsible for translation from French to Bamabara (the local language). The purpose and significance of the project was discussed with the translators in order to ensure as much as possible that they conducted a culturally accurate translation. The test administrators were further trained on the importance of objective and consistent delivery of the questionnaire, and observed by our team. The test was multiple choice in nature. Due to illiteracy levels, picture symbols (box, moon, smile, star) represented each choice. As this was in part a pilot study, we did not seek separately to test the validity of each question and the questionnaire as a whole.

In two different villages, 200 individuals consented for participation in our study within 48 hours of the malaria trial's initial consent process. Groups of six to 14 participants were brought to each village's school, and seated at desks no less than 4 feet away from one another to prevent sharing of information. The test instructions were then read. Two screening questions (with obvious answers) were presented to ensure participants' ability to understand and use the multiple-choice

Table 1 Results of questionnaire

Question Topic	% Responses Village R *N* = 78*	% Responses Village U *N* = 85	Total combined % correct
1) Voluntary participation	*N* = 67	*N* = 85	57%
a. Village elder	45% (30)	9% (8)	
b. Yourself	**21% (14)**	**85% (72)**	
c. Study team	21% (14)	5% (4)	
d. Spouse	13% (9)	1% (1)	
	R = 2	*R* = 1	
2) Compensation	*N* = 65	*N* = 85	**44%**
a. Money and checkups	8% (5)	13% (11)	
b. Malaria medicine and checkups	18% (12)	27% (23)	
c. Food and checkups	**28% (18)**	**56% (48)**	
d. Checkups only	46% (30)	4% (3)	
	R = 2	*R* = 1	
3) Withdrawal criterion	*N* = 59	*N* = 85	**10%**
a. At any time	**12% (7)**	**9% (8)**	
b. With scientist's permission	34% (20)	80% (68)	
c. Village leader's permission	20% (12)	6% (5)	
d. Spouse's permission	34% (20)	5% (4)	
	R = 4	*R* = 2 (low)	
4) Withdrawal consequence	*N* = 37	*N* = 85	**44%**
a. Checkups, but no food or money	27% (10)	45% (38)	
b. Nothing and no healthcare access	11% (4)	6% (5)	
c. Punished and fined	13% (5)	7% (6)	
d. Nothing but healthcare access	**49% (18)**	**42% (36)**	
	R = 1	*R* = 2	
5) Study versus treatment	*N* = 30	*N* = 85	**26%**
a. Determine cause of malaria	53% (16)	26% (22)	
b. Provide village with medicine	13% (4)	22% (19)	
c. Study malaria/anemia incidence	**20% (6)**	**28% (24)**	
d. Cure malaria in village	13% (4)	24% (20)	
	R = 2	*R* = 1	
6) Study administration	*N* = 65	*N* = 85	**66%**
a. Malian and U.S. scientists	**43% (28)**	**84% (71)**	
b. Villagers	32% (21)	6% (5)	
c. French government	12% (8)	8% (7)	
d. Foreign company	12% (8)	2% (2)	
e. Local political party	0% (0)	0% (0)	
	R = 1	*R* = 1	
7) Randomization and placebo	*N* = 29	*N* = 85	**68%**
a. Past medical history	24% (7)	12% (10)	
b. Randomly	**62% (18)**	**71% (60)**	
c. Social position	0% (0)	2% (2)	
d. Current health	14% (4)	15% (13)	
	R = 1	*R* = 1	
8) Side effects	*N* = 62	*N* = 85	**7%**
a. Risks and side effects	**10% (6)**	**6% (5)**	
b. Is a vaccine for life	27% (17)	25% (21)	
c. No side effect	18% (11)	28% (24)	
d. Will correct malnourishment	45% (28)	41% (35)	
	R = 4	*R* = 4	
9) Lay scientific knowledge	*N* =78	*N* = 85	**73%**
a. Vegetation	14% (11)	6% (5)	
b. Poor nutrition	9% (7)	5% (4)	
c. Sadness	10% (8)	6% (5)	
d. Night birds	4% (3)	1% (1)	
e. Mosquitos	**63% (49)**	**82% (70)**	
	R = 1	*R* = 1	

*Number eligible who answered screening questions adequately. See text.
N = number of interpretable responses for each question, *R* = Rank of correct answer (independent of percentage correct, when ordered from most often chosen answer [1 = 1st] to least often [eg, 4 = 4th], when compared with other answer choices).

format. Any participant who chose an incorrect answer for the first sample question had their mistake explained to them, and was invited to try the second practice question. Regardless of performance on the first sample question, any participant who did not answer the second sample question correctly had his or her responses excluded in entirety from the final results. Of the remaining individuals included, any items not answered, incomprehensibly marked or double marked, were excluded individually from final analysis. These exclusions explain the differences in final sample size between the two villages, and in number of respondents on each question. In village R, on several questions, participants did not answer or mistakenly double marked the questionnaire, reflecting in part the lower level of education and foreignness of testing in this village. The translator administering the questionnaire was the only individual who talked during the administration of the questionnaire. To minimize sharing of information, questions by participants were limited.

Study sites

To protect identity, the villages will be referred to as "Village R" (for rural) and "Village U" (for urban). Village R is a rural, agrarian village, 2.5 hours from the Malian capital of Bamako. Its population is approximately 8000; its economy is agrarian subsistence farming, and it has no electricity. Greater than 90% of consenting parents who took part in the study had not attended school, and were illiterate. Participants from Village R involved in the questionnaire were 92% male, and had, on average, 2.5 children enrolled in the larger study. These demographics for Village R suggest that the male population works in close proximity to the village (in farming) and is thus able to be present as head of household, and that there are relatively larger numbers of children per family as compared with Village U.

Village U is a suburb of the capital city of Bamako (25 minutes from the city center, directly off Mali's main highway). Its population is approximately 13 000 and its economy is commerce-oriented. It has electricity and telephones in over 60% of households. Since the majority of the men work in the city, 83% of the consent for children to participate in the vaccine study was given by the female head of household. Of the consenting individuals (83% female, 13% male), 67% had primary education and 70% were literate to some degree. In general, the degree of education and political awareness was greater in Village U than Village R. Many of the villagers in Village U spoke French, but Bambara was the primary language. Village U's consenting parents had, on average, 1.5 children enrolled in the study, indicating smaller family size. The expendable income per family, as demonstrated by the presence of clothing and accessories, was substantially higher than in Village R, and access to "modern" goods and current news was facilitated by the village's urban proximity.

In each village, 100 consenting individuals initially participated in our study and were questioned. In Village R, 100 out of 103 eligible parents were questioned, with 78 participants eligible following screening questions. In Village U, 100 out of 167 eligible parents were questioned, with 85 participants eligible.

Statistical methods

We present results in this study both as absolute percentages of participants who answered correctly, as well as rank numbers comparing how the correct answer choice faired against the other, incorrect "decoy" answer choices. Statistical analyses were performed using both a chi-squared and a binomial test. The chi-squared statistic tested the null hypothesis that respondents selected any answer choice with equal probability without regard to the correct answer (pure guess work), whereas the binomial z-statistic tested the broader null hypothesis that respondents selected the correct answer with probability 0.20 (when there were five choices) or 0.25 (when there were four choices) irrespective of their distribution across other incorrect choices. For example, Question 1 in Village R gives a chi-squared P-value of 0.005 and a binomial P-value of 0.22. The chi-squared P-value of <0.005 allows one to reject the null hypothesis that participants were guessing at all answers, whereas the binomial P-value of 0.22 suggests that the proportion of people answering correctly (21%) is not significantly different from what we would expect by chance (25%). Because the null hypotheses are nested (ie, pure guesswork in all choices implies guesswork on the correct choice), we used a "closed" test procedure, whereby one tests the hypothesis of guesswork on the correct choice if and only if one first rejects the hypothesis of pure guesswork in all choices (by the chi-squared test at the 0.05 level). It is easy to demonstrate that this closed test procedure controls the probability of committing one or two type I errors at the 0.05 level per item (see more generally Marcus *et al.* [8] and Hochberg and Tamhane [9]). If the chi-squared test was not significant at the 0.05 level, the procedure stopped – ie, we did not consider the binomial test for this item. If the chi-squared test was significant, we proceeded with the binomial test at the 0.05 level, to address whether or not the departure from pure guesswork favored

the correct answer. In addition, we also calculated the 95% confidence interval for the percentage of correct answers based on the method illustrated by Daniel [10].

Results

The survey results are reported in Tables 1 and 2. As previously noted, 22 of 100 participants in Village U and 15 of 100 in Village R could not understand the multiple choice format and were deemed ineligible for this survey. Almost all eligible participants answered every question in Village U, whereas Village R had highly variable usable response rates, between 37% (Q7) and 100% (Q9). This wide range may have occurred due to lower level of education, and consequent foreignness of testing. The chi-squared test rejected the null hypothesis ($P < 0.005$) for all items in both villages separately, indicating an overall pattern not consistent with guessing, except for Questions 3 ($P < 0.05$ in Village R and 5 ($P = 0.87$) in Village U. All of the binomial results were significant, indicating a percentage for the correct answer that statistically differed from chance, except for questions about voluntary participation (Q1), and compensation (Q2) in Village R, and treatment versus research (Q5) in both villages, in which the percentage of correct responses were 20–28% (close to chance). The percentage of correct answers exceeded 50% for five questions in Village U, and two questions in Village R. The correct answer was the most frequent one chosen for six questions in Village U and four questions in Village R. The percentage of correct answers was statistically significantly higher in Village U than Village R for four of the questions; voluntary participation (85% versus 21%), compensation (56% versus 28%), study administration (84% versus 43%) and knowledge about the cause of malaria (82% versus 63%).

Discussion

While deficits with consent comprehension exist universally, the results here illustrate the relative degree of miscomprehension between demographically different towns in West Africa and, more importantly, miscomprehension in the developing world, relative to industrialized nations. By focusing on those areas with low percentages of correct responses, problematic areas are best identified. As poor as these results are, it is likely that the percentages of correct answers observed here are high relative to the population sampled, since 15% of questioned adults in Village U and 22% in Village R could not reliably use a multiple choice format, and were ineligible for this survey. However, all of these individuals had provided consent for the parent study.

The differences between Village R and Village U can be attributed to several factors. In general, participants from Village R answered incorrectly more often than those from Village U. The most likely reason for Village U's better performance, as described above, is Village U's much higher percentage of literate adults and school attendance. While demographics of age and sex invariably influences response, the sample size impeded our ability to control for these factors formally.

The most troublesome aspect of these results is not just the extent of miscomprehension in certain areas, but the relative degree of miscomprehension when compared to studies conducted in industrialized nations, particularly concerning withdrawal criteria and side effects. As described above, studies conducted in the United States and Europe have illustrated that between 20% and 33% of participants miscomprehend withdrawal criterion [4,5], while our study illustrates that 90% of participants miscomprehended withdrawal criterion. Moreover, the other three answer options for the question on voluntary withdrawal – that the study team, the village chief, or one's spouse must give permission

Table 2 Statistical analysis of percentage of correct answers on questionnaire. The binomal *P*-value tests whether the reported percentage deviates from the percentage expected by chance (ie, 25% for four-response questions and 20% for five-responses)

	Village R		Village U	
Question	*P*-value	Percent correct (95% CI)	*P*-value	Percent correct (95% CI)
1) Voluntary participation	0.22	0.21 (0.11, 0.31)	<0.005	0.85 (0.77, 0.93)
2) Compensation	0.31	0.28 (0.17, 0.39)	<0.005	0.56 (0.46, 0.66)
3) Withdrawal criterion	0.01	0.12 (0.04, 0.20)	<0.005	0.09 (0.03, 0.15)
4) Withdrawal consequence	<0.005	0.49 (0.33, 0.65)	<0.005	0.42 (0.32, 0.52)
5) Study versus treatment	0.26	0.20 (0.06, 0.34)	0.25	0.28 (0.18, 0.38)
6) Study administration	<0.005	0.43 (0.31, 0.55)	<0.005	0.84 (0.76, 0.92)
7) Randomization and placebo	<0.005	0.62 (0.44, 0.80)	<0.005	0.71 (0.61, 0.81)
8) Side effects	<0.005	0.1 (0.02, 0.18)	<0.005	0.06 (0.01, 0.11)
9) Lay scientific knowledge	<0.005	0.63 (0.53, 0.73)	<0.005	0.82 (0.74, 0.90)

for a child to withdraw – imply a perceived loss of self-determination to withdraw from the study. A consenting parent's belief that third party permission is required to withdraw their child from the study inherently implies the child may be kept in the study despite the wishes of the parents or child.

The miscomprehension of drug side effects is also troubling. While studies conducted in industrialized nations demonstrated 38% of participants miscomprehending the existence of side effects [6], in Village U and Village R, 93% of residents failed to identify the existence of side effects with study drugs. Misunderstood study risks have critical ethical consequence. Other investigators have noted that participants consistently identify the existence of risks as the major impediment to participating in research trials [11]. Without fully understanding a study's side effects, a participant cannot make an informed decision as to the degree of risk he/she is willing to accept by participating. This trend of miscomprehension of side effects in developing nations has been noted by others [6,12], but the present data help provide a quantitative assessment of this important phenomenon.

A final area of common miscomprehension involved differentiation between study and treatment. Question 5, evokes the so-called "therapeutic misconception" [13,14], in which participants mistake experimental research for effective treatment. In Village R, 80% failed to understand that researchers were providing an investigational agent, as opposed to therapy. Though this miscomprehension may also exist in Village U, the statistical distribution of responses was consistent with participants guessing randomly, which is not reassuring, either. As described above, a lower level of education and literacy may correspond with a greater difficulty understanding key aspects of research. A second possibility may also be involved in Village R's low understanding of voluntary participation (Question 1). In a communal society, many believe that the village chief or government directs actions. Participants might presume a leader's benevolence – that the village chief or government would only have citizens participate if the trial was therapeutic. Other studies on trials in the developing world have suggested, too, that the idea of informed consent may be inappropriate in communal societies such as those in Mali because consent can never be truly "voluntary" in a society that values community above individuality [15]. Whatever the reason is for this misconception, and the degree to which it exists in Village U as well, the ethical dilemma of patients mistakenly expecting benefit from a no-benefit study is apparent and should be taken seriously in both rural and urban settings.

This study has several potential limitations. We observed the consent process in both villages, however did not formally assess its inherent quality directly, but rather indirectly through participants' understanding of it. Although the process was consistently delivered by the same researchers in both villages, both cultural and language barriers make an accurate full assessment of the process itself difficult. In addition, different translators were used in each of the two villages, making a complete statistical comparison between the two villages difficult. However, the two translators received the same instructions and training concerning this study and the procedures involved. Moreover, despite differences in translation, the uniformity of ranking of responses for each question between villages suggests certain trends in miscomprehension and a generally consistent translation effort.

The potentially threatening nature of "exams" in schools, particularly for those who are illiterate and had very little experience of schools may also have affected results. The data here cannot be assumed to be wholly generalizable to other developing nations outside West Africa. However, this study suggested a high degree of miscomprehension relative to industrialized nations that highlights the need to investigate further these areas in other countries and contexts as well. As other cultures have differing understandings of autonomy and individuality, Western standards in the consent process may be somewhat inapplicable to other countries, because of cultural reasons.

The present data do not address whether and to what degree Western concepts of informed consent are valid in the developing world. On the one hand, critics argue that, "informed consent is neither necessary nor sufficient for ethical clinical research" [16], and that one need only the "capacity to understand," not a true understanding, for informed consent to be valid [17]. Still others write that, "the premise of informed consent as a rational decision making process … may be perceived as an ideal in the nature of a myth" [18]. Nonetheless, current Western bioethical standards maintain at least the ideal of informed consent as a critical aspect of ethical clinical research. Thus, a strong argument can be made that investigators working in developing nations have an ethical responsibility to insure that their research subjects are as well-informed as possible. These results also underscore the need to consider innovative and creative approaches to achieve that. Despite cultural differences regarding informed consent, it appears to be appropriate to err on the side of over-informing study participants, so as to minimize the likelihood of participation decisions being made based on faulty information. Adverse events stemming from miscomprehension occurring in a trial jeopardize not only that trial, but also the larger relationship between foreign research teams, foreign science, and developing nations.

This study suggests several areas for future research. First, qualitative methods can help clarify several of the issues raised here as to how participants understand the informed consent process. For example, participants may feel that they cannot withdraw at any time because either they did not understand that this option was presented to them by the investigator, or they did not believe (due to cultural attitudes and norms) that such autonomy is in fact possible within the context of their culture. Linguistically, future research can assess why therapeutic misconception remains such a difficult problem, and whether ways may exist to address this misconception, within these villages own language, that may better clarify the differences between treatment and research.

This study illustrates degrees of miscomprehension in developing nations (that can be viewed in comparison with other studies conducted in the industrialized world), specific areas of miscomprehension in these countries, and needs for future research. These data suggest certain areas of deficits and can help investigators in tailoring their informed consents to address these areas of miscomprehension. These data can also aid in increasing understandings of what approaches toward informed consent might be most ethically and logistically appropriate. Moreover, studies such as this one can benefit IRBs reviewing similar projects to ensure as much comprehension of informed consent as possible, as reflected in changes in consent forms and procedures as well as periodic assessments of the quality of the consent process.

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Appendix 1: Questionnaire

1) The participation of your child in the study—
- a) — Was decided upon by the village leaders as necessary.
- b) — **Was decided upon by you and your husband and is completely optional. If you do not want your child enrolled, your child need not participate.**
- c) — Was decided upon by the scientists and doctors.
- d) — Was decided upon by your husband.

2) As compensation for participating in the study, your family and your child will receive—
- a) — A small amount of money in addition to weekly physical checkups for your child.
- b) — Malaria medicine everyday, money, and weekly checkups for your child.
- c) — **A small amount of food (rice, millet or sugar) in addition to weekly checkups for your child.**
- d) — Weekly checkups, but nothing more.

3) Once the study has begun—
- a) — **You may remove your child from the study at any time.**
- b) — You may remove your child from the study only if the study organizers say it is OK.
- c) — You may remove your child from the study with the permission of village leaders.
- d) — You may remove your child from the study with permission from your husband.

4) If you decide for your child to drop out of the study—
- a) — Your child will still be given weekly checkups, but no food or money.
- b) — You will be given nothing – including no access to healthcare services for your children.
- c) — You will be fined and punished.
- d) — **You will be given nothing, but will always have access to healthcare in case of a medical problem or emergency.**

5) The purpose of this project is—
- a) — To determine the cause of malaria.
- b) — To provide your village with malaria medications and health care.
- c) — **To study the amount of malaria and anemia in your village and possibly develop a cure for malaria.**
- d) — To provide your village with a cure for malaria.

6) This project is run by—
- a) — **Scientists and doctors working for the governments of Mali and the United States of America.**
- b) — Your village health and medical officials.
- c) — The French government.
- d) — A foreign company.
- e) — Adama (local political party).

7) Children are selected to take this medicine—
- a) — Based on a past medical history.
- b) — **By random assignment – like drawing lots.**
- c) — Based on social position of family.
- d) — Based on current health of child.

8) The medicine that some children receive—
- a) — **Will prevent malaria right now, but carries a small risk of some side effects such as rash, nausea, or other problems.**
- b) — Is a vaccine which will prevent malaria for the rest of your child's life.
- c) — Carries no known side effect.
- d) — Will correct nutritional deficiencies and other health problems your child might now have.

9) Malaria is caused by—
- a) — Vegetation.
- b) — Poor nutrition.
- c) — Lack of sleep, excessive crying, and excessive sadness.
- d) — A bird flying over you during the night.
- e) — **The bite from an infected mosquito.**