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Short Communication

Using the influenza vaccine as a mild, exogenous inflammatory challenge: When does inflammation peak?

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ABSTRACT

Background: The influenza vaccine has shown promise as a mild, exogenous inflammatory challenge, but use of this model is limited by lack of knowledge about the timing of the inflammatory response. This study was designed to characterize the time-course of the acute inflammatory response and explore psychological and behavioral predictors of that response.

Methods: Twenty-one young, healthy individuals were recruited to receive the annual influenza vaccine. Serial blood samples were collected immediately before, and 24, 48, and 72 h following influenza vaccination. Interleukin (IL)-6 concentrations were assayed at each time-point and psychological and behavioral factors (anxiety and depressive symptoms, sleep disturbance, and childhood adversity) were assessed at baseline.

Results: Significant elevations in IL-6 were observed at 24 h post-vaccination (mean increase = 0.70 pg/mL, Cohen's d = 0.54, $p = .018$)), with 61.9% of participants exhibiting peak concentrations at that time point, $\chi^2 = 22.54$, $p < .001$, $\eta = 0.52$. In exploratory analyses, sleep disturbance was associated with greater increases in IL-6 at 24 h.

Conclusions: By identifying the peak IL-6 response to influenza vaccination among a sample of young, healthy individuals, these findings support the use of the influenza vaccine in future PNI research. This vaccine model can be used to examine the impact of mild inflammatory challenges on the brain and behavior, and to identify psychological and behavioral factors (e.g., anxiety, sleep) that modulate inflammatory reactivity.

1. Introduction

The field of psychoneuroimmunology (PNI) has a rich tradition of investigating how the immune and central nervous systems interact to influence physical and mental health (Ader, 2007). Vaccinations provide a unique opportunity to study how mild immune activation influences psychological and behavioral processes. Unlike endotoxin administration, which results in 100-fold increases in circulating proinflammatory cytokines (Eisenberger et al., 2009), influenza and typhoid vaccines lead to increases in circulating cytokines in the range of 1 pg/ml (Kuhlman et al., 2018). This low level activation more closely resembles what is observed in the context of acute and chronic stress (Brydon et al., 2008; Steptoe et al., 2007), as well as among certain clinical populations (e.g., individuals undergoing cancer treatment) (Bower et al., 2009), and thus provides a compelling approach to understanding the inflammation-related effects of those types of exposures. An additional benefit of the influenza vaccine is its widespread availability, making it a particularly attractive model for interrogating effects of peripheral inflammation in the general public and in vulnerable populations. Previous research has demonstrated that influenza vaccination leads to short-term changes in inflammatory activity, as indicated by increases in circulating concentrations of IL-6 and C-reactive protein and upregulation of inflammatory gene expression (Kuhlman et al., 2018; Christian et al., 2015; Bucasas et al., 2011). Another key advantage of the influenza

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vaccine is that, unlike endotoxin, it results in very little, if any, physical sickness (e.g., fever, nausea); therefore, the influence of inflammation on behavior can be studied in the absence of this confound. Thus, the influenza vaccine is an exciting paradigm with great potential for use in PNI research.

Despite its methodological promise, the time course of the inflammatory response to influenza vaccination has yet to be fully characterized. A handful of studies have employed serial blood sampling to examine changes in circulating cytokines and/or inflammatory gene expression following influenza vaccination and have found peaks on either days 1, 2, or 3 (Christian et al., 2011, 2013, 2015; Bucasas et al., 2011; Tsai et al., 2005a). Based on the existing literature, it is unclear when inflammation peaks post-vaccination, a critical question for future research using this paradigm. Thus, the goal of this study was to evaluate the timing and extent of the inflammatory response to influenza vaccination, with a focus on late adolescents/early adults. We believe this model has great potential utility in vulnerable populations for whom current approaches such as endotoxin would not be feasible. Serial blood samples were collected from healthy individuals before and at 1, 2, and 3 days post vaccination with the influenza vaccine. We focused on circulating concentrations of IL-6, a key proinflammatory cytokine that is influenced by influenza vaccination and has been linked with neural and behavioral changes following administration of endotoxin and the typhoid vaccine (Christian et al., 2011; DellaGioia and Hannestad, 2010; Tsai et al., 2005b). A second, exploratory goal was to examine psychological and behavioral factors that may influence the inflammatory response. We focused on four factors that have previously been shown to modulate the inflammatory response to challenge: anxiety and depressive symptoms, sleep disturbance, and childhood adversity (Glaser et al., 2003; Irwin et al., 2019; Carpenter et al., 2010).

2. Methods

2.1. Participants

A sample of 21 healthy young adults were recruited at the University of California, Los Angeles (UCLA). Participants were eligible if they were 1) between the ages of 18–22, 2) eligible to receive the influenza vaccination at the student health center), and 3) had not yet received the 2018/2019 influenza vaccine. Participants were ineligible if they 1) had an allergy to any agent used to develop the influenza vaccine; 2) had current symptoms of influenza or upper respiratory illness (e.g., coughing, fever); 3) had a current psychiatric diagnosis or any major medical condition including diabetes, asthma, cancer, juvenile rheumatoid arthritis; or 4) reported regular use of steroid medications.

2.2. Study procedure

Participants completed four study visits across four consecutive days to observe the change in IL-6 from pre-to post-vaccine. All study visits occurred in the morning (8:30am–11:30am) to account for circadian fluctuations in IL-6. At the baseline visit, participants provided informed consent, completed questionnaires, and had their blood drawn to assess pre-vaccination levels of IL-6. They were then escorted to the student health center to receive their 2018/2019 influenza vaccination. In order to capture the time-course of the inflammatory response to the vaccine, all participants returned to the lab for follow-up blood draws 24, 48, and 72 h later. For each participant, efforts were made to schedule appointments at the same time each morning. On average, blood draws were completed within 30 min prior to vaccine and 24.10 h (SD = 0.81 h), 48.01 h (SD = 0.42 h), and 71.33 h (SD = 0.99 h) after vaccination. At each study visit, participants had their temperature taken. Participants were compensated $150 for completing all four study visits. All study procedures were approved by the UCLA Institutional Review Board.

2.3. Measures

At the baseline visit, participants reported on their biological sex, race and ethnicity, and age, and whether they had received the influenza vaccine the previous year. Childhood adversity was determined using a standardized list of adverse childhood experiences (Felitti et al., 1998). *Sleep disturbance* over the last 2 weeks was assessed using the Insomnia Severity Index (ISI) (Morin et al., 2011). *Depressive symptoms* over the past 2 weeks were assessed using the Patient Health Questionnaire (PHQ-8) (Kroenke et al., 2001). *Anxiety symptoms* over the past 2 weeks were assessed using the Generalized Anxiety Disorder 7-item Scale (GAD-7) (Spitzer et al., 2006). Blood samples were collected through venipuncture by a licensed phlebotomist from all participants before vaccination and at 24, 48, and 72 h post-vaccination; we were unable to collect a blood sample for one participant at day 3. Blood was immediately centrifuged for the collection of plasma, which was then stored at −80° until assayed. Once all samples were collected, IL-6 concentrations were determined by ELISA (R&D Systems, Minneapolis, Minn), with all samples assayed in duplicate (interassay CV = 4.61%, intraassay CV = 3.22%). IL-6 levels for the entire sample were within the normal physiological range (0.32–12.10 pg/mL). All assays were conducted at the UCLA Cousins Center for Psychoneuroimmunology.

2.4. Statistical analyses

The primary goal of this study was to identify the time point at which the majority of subjects exhibited the highest levels of IL-6. Thus, descriptive statistics were used to determine the number and percentage of individuals who exhibited their peak IL-6 response at each time point. We used a χ^2 distribution test to determine whether peak IL-6 concentrations were disproportionately likely to occur on a particular study day.

We also examined mean concentrations of IL-6 at each point to evaluate the magnitude and trajectory of the IL-6 response. A multilevel model with IL-6 nested within people was used to determine whether mean IL-6 varied as a function of time, to examine pairwise comparisons between baseline and post-vaccination time points, and to determine effect sizes. For these models, the intercept and time were included as random effects. Exploratory analyses examined psychological and behavioral factors as predictors of the peak inflammatory response to vaccine using linear regression models and controlling for baseline levels of IL-6. Levels of IL-6 were log-transformed to correct for non-normality.

3. Results

Descriptive statistics for demographic, psychological and behavioral measures are presented in Table 1. All 21 enrolled participants completed

Table 1
Characteristics of the sample.

Characteristics	N = 21
Female (N, %)	12, 57%
Age (years) (Mean (SD))	19.4 (1.25)
Ethnicity/Race	
Non-Hispanic White (N, %)	12, 57.1%
Non-Hispanic Black (N, %)	2, 9.5%
Asian (N, %)	7, 33.3%
Adverse Childhood Experiences (ACE) (Mean (SD))	1.0 (1.16)
Insomnia Severity Index (ISI) (Mean (SD))	6.6 (4.38)
Depressive Symptoms (PHQ-8) (Mean (SD))	4.7 (4.42)
Anxiety Symptoms (GAD-7) (Mean (SD))	4.6 (4.28)
IL-6 (pg/mL) (Mean (SD) [range])	
Baseline	1.66 (1.45) [0.32–5.66]
24 h	2.36 (2.16) [0.41–10.92]
48 h	1.70 (2.49) [0.34–12.10]
72 h	1.29 (1.32) [0.42–6.59]

all four study visits. Of these 21 participants, 57% were female, on average 19 years old, and the sample was 60% non-Hispanic White and 33% Asian. Participants reported low levels of insomnia, anxiety, and depressive symptoms, which was expected given our exclusion criteria. Eleven participants had received the previous year's influenza vaccination, 9 had not, and one did not remember.

Mean concentrations of IL-6 at each assessment are shown in Table 1 and Fig. 1. The highest mean levels of IL-6 were observed at 24 h post-vaccination, with a mean increase of 0.70 pg/ml from baseline to 24 h. Further, the majority of participants (61.9%) exhibited their highest levels of IL-6 at 24 h post-vaccination; 23.8% exhibited their highest IL-6 values at baseline, 4.8% peaked at 48 h, and 9.5% peaked at 72 h (see Fig. 1). Results of the χ^2 test indicated that these peaks were not equally distributed across the study assessments χ^2 () = 22.54, $p < .001$, $\eta = 0.52$.

We next employed a mixed model with log IL-6 nested within people to examine changes in IL-6 across the assessment period and generate effect size estimates. Results showed a significant effect of time on mean log IL-6 levels ($F(3, 20) = 13.43$, $p < .001$). Pairwise comparisons between baseline and each post-vaccination assessment yielded the following effect size estimates: Cohen's $d = 0.54$ at 24 h, 0.13 at 48 h, and 0.24 at 72 h. Changes in log IL-6 levels from baseline were only significantly different from 0 at 24 h ($p = .018$). The effect of time on IL-6 remained significant after controlling for awakening time ($F(3, 20) = 15.90$, $p < .001$).

There was substantial variability in the extent of IL-6 changes following vaccination; change in IL-6 from baseline to 24 h ranged from −2.05 to 9.26 pg/mL with a standard deviation of 2.20 pg/mL. We examined baseline psychological and behavioral predictors of change in IL-6 at 24 h, controlling for baseline levels of IL-6. Greater sleep disturbance ($\beta = 0.40$, $p = .031$) predicted greater IL-6 change from baseline to peak (24 h). Additionally, more anxiety symptoms marginally predicted greater IL-6 changes from baseline to 24 h ($\beta = 0.34$, $p = .078$). Neither adverse childhood experiences nor depressive symptoms were significantly associated with IL-6 changes following vaccination (*ps* > .64).

Additional analyses were conducted to identify predictors of vaccine non-response (i.e., highest concentrations of IL-6 at baseline). Receiving last year's vaccine was not associated with response to the current year's vaccine ($\chi^2 = 0.61$, $p = .62$). In addition, demographic (age, sex) and psychosocial (sleep disturbance, adverse childhood events, depressive and anxiety symptoms) variables were not associated with non-response to the current year's vaccine (all ps > .17).

4. Discussion

This study aimed to characterize the timing of peak acute inflammatory response to influenza vaccination. Unlike other exogenous inflammatory stimuli used in PNI research (e.g., endotoxin administration),

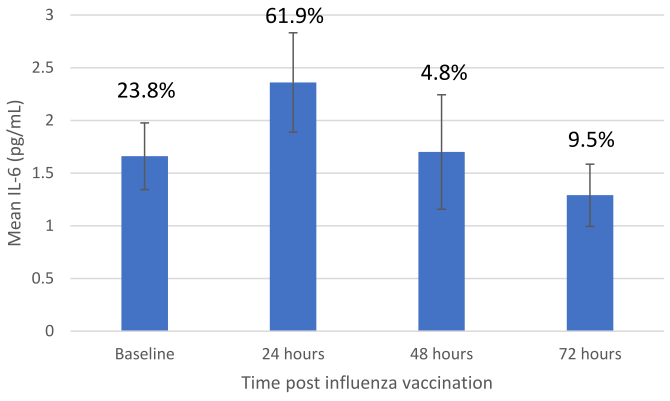

Fig. 1. Mean IL-6 concentrations in pg/mL, standard errors, and percentages of individuals who exhibited their highest levels of IL-6 are presented at each study visit.

the influenza vaccine is a widely distributed vaccine that nearly 50% of the general adult population receives annually and can be safely administered to vulnerable populations (CDC, 2018–2019) (Center for Disease Control and Prevention, 2019). This makes the influenza vaccine an attractive and feasible model for interrogating short-term effects of inflammation on mood and behavior. Although the influenza vaccine has been used as an immune probe in previous research (Christian et al., 2011; Tsai et al., 2005b; McDade et al., 2015; Posthouwer et al., 2004), no study to date has systematically interrogated the time course of the acute inflammatory response within this vaccination model in healthy young adults.

Through sampling blood immediately before, 24, 48, and 72 h following vaccination, we identified 24 h as the time of peak inflammatory response for the majority (61.9%) of participants, as measured by plasma IL-6 concentrations. On average, IL-6 increased by 0.70 pg/mL at this time point. This increase is comparable to or larger than that seen in earlier studies of influenza vaccination conducted by our group (mean increase in IL-6 from baseline to 24 h post vaccination = 0.33 pg/mL) (Kuhlman et al., 2018) and others (mean increase in IL-6 from baseline to 24 h = 0.70 pg/mL) (Tsai et al., 2005b). Results also document considerable variability in the IL-6 "peak" response at 24 h post vaccination. Importantly, this variability highlights the influenza vaccine's utility as a probe for examining factors that might influence the inflammatory response itself, as well as the degree to which inflammation leads to changes in mood and behavior. We have previously shown that early life adversity modulates the association between IL-6 response to influenza vaccination and depressive symptoms (Kuhlman et al., 2019). Here, we found that sleep disturbance was associated with an enhanced inflammatory increase following vaccination, which converges with findings from an endotoxin study in which sleep disturbance was found to modulate endotoxin-stimulated depressed mood (Cho et al., 2016).

Although the majority of participants showed a peak response at 24 h, almost 30% showed either a delayed response at 48 or 72 h post-vaccination or no elevation in IL-6 after vaccination (highest levels of IL-6 at baseline, "non-responders"). Indeed, approximately one-quarter of participants exhibited their highest levels of IL-6 at the baseline visit. These findings are consistent with our previous study of influenza vaccination, which found that 21.95% of participants showed their highest levels of IL-6 before vaccination (Kuhlman et al., 2018). We considered a number of factors that might have contributed to the lack of IL-6 response in this sample, including receipt of the previous year's influenza vaccine as well as demographic and psychosocial factors. None of these variables were associated with responder status. It is possible that elevated concentrations of IL-6 at baseline were due to stress resulting from the initial blood draw, which may have obscured smaller increases in IL-6 following vaccination. Of note, IL-6 levels are less stable than other inflammatory markers such as CRP; therefore, future studies should investigate the time course of other inflammatory markers to further illuminate differences in response and non-response to influenza vaccination.

Results from the current study can inform future research using the influenza vaccine model, demonstrating that peak responses to vaccination typically occur at 24 h post vaccination in healthy young adults. Study limitations are also important to note. First, we did not include a control group; therefore, we cannot conclude that changes in IL-6 from pre-to post-vaccination were due solely to influenza vaccination. Second, our findings are specific to circulating levels of IL-6 and may not generalize to other inflammatory markers. Third, it is possible that the timing of peak elevations in IL-6 observed in our young, healthy sample may differ from those that occur in other populations. Fourth, although the levels of IL-6 observed following vaccination are similar to those observed in certain chronic inflammatory conditions, influenza vaccination is not a model of chronic inflammation; the immune drivers of acute and chronic inflammation are quite different and their impact on the brain and behavior may also differ (Calder et al., 2013). Finally, the current findings do not address the health relevance of a higher (or

lower) inflammatory response. Future studies should evaluate whether IL-6 and other inflammatory responses to influenza vaccination are associated with downstream effects on antibody responses and protection against infection and illness. Overall, our findings support the use of influenza vaccination as a probe for mild inflammatory activity and help to identify the optimal time point for capturing peak responses to inflammation in this promising model.

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Declaration of competing interest

None.

References

Ader, R., 2007. Psychoneuroimmunology, fourth ed. Elsevier/Academic Press.

Bower, J.E., Ganz, P.A., May, L.T., et al., 2009. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin. Canc. Res. 15 (17), 5534–5540. https://doi.org/10.1158/1078-0432.CCR-08-2584.

Brydon, L., Harrison, N.A., Walker, C., Steptoe, A., Critchley, H.D., 2008. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol. Psychiatr. 63 (11), 1022–1029. https://doi.org/10.1016/j.biopsych.2007.12.007.

Bucasas, K., Franco, L., Shaw, C., et al., 2011. Early patterns of gene expression correlate with the humoral immune response to influenza vaccination in humans - PubMed. J. Infect. Dis. 203 (7), 921–929. https://pubmed.ncbi.nlm.nih.gov/21357945/. (Accessed 11 May 2020). Accessed.

Calder, P.C., Ahluwalia, N., Albers, R., et al., 2013. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br. J. Nutr. 109 (S1), S1–S34. https://doi.org/10.1017/S0007114512005119.

Carpenter, L.L., Gawuga, C.E., Tyrka, A.R., Lee, J.K., Anderson, G.M., Price, L.H., 2010. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology 35 (13), 2617–2623. https://doi.org/10.1038/npp.2010.159.

Center for Disease Control and Prevention, 2019. Flu vaccination coverage, United States, 2018–19 influenza season | FluVaxView | seasonal influenza (flu) | CDC. Published. https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm. (Accessed 12 May 2020). Accessed.

Cho, H.J., Eisenberger, N.I., Olmstead, R., Breen, E.C., Irwin, M.R., 2016. Preexisting mild sleep disturbance as a vulnerability factor for inflammation-induced depressed mood: a human experimental study. Transl. Psychiatry 6 (3), 750. https://doi.org/10.1038/tp.2016.23.

Christian, L.M., Iams, J.D., Porter, K., Glaser, R., 2011. Inflammatory responses to trivalent influenza virus vaccine among pregnant women. Vaccine 29 (48), 8982–8987. https://doi.org/10.1016/J.VACCINE.2011.09.039.

Christian, L.M., Porter, K., Karlsson, E., Schultz-Cherry, S., Iams, J.D., 2013. Serum proinflammatory cytokine responses to influenza virus vaccine among women during pregnancy versus non-pregnancy. Am. J. Reprod. Immunol. 70 (1), 45–53. https://doi.org/10.1111/aji.12117.

Christian, L.M., Porter, K., Karlsson, E., Schultz-Cherry, S., 2015. Proinflammatory cytokine responses correspond with subjective side effects after influenza virus vaccination. Vaccine 33 (29), 3360–3366. https://doi.org/10.1016/j.vaccine.2015.05.008.

DellaGioia, N., Hannestad, J., 2010. A critical review of human endotoxin administration as an experimental paradigm of depression. Neurosci. Biobehav. Rev. 34 (1), 130–143. https://doi.org/10.1016/j.neubiorev.2009.07.014.

Eisenberger, N.I., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2009. An fMRI study of cytokine-induced depressed mood and social pain: the role of sex differences. Neuroimage 47 (3), 881–890. https://doi.org/10.1016/j.neuroimage.2009.04.040.

Felitti, V.J., Anda, R.F., Nordenberg, D., et al., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the adverse childhood experiences (ACE)study. Am. J. Prev. Med. 56 (6), 774–786. https://doi.org/10.1016/j.amepre.2019.04.001.

Glaser, R., Robles, T.F., Sheridan, J., Malarkey, W.B., Kiecolt-Glaser, J.K., 2003. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. Arch. Gen. Psychiatr. 60 (10), 1009–1014. https://doi.org/10.1001/archpsyc.60.10.1009.

Irwin, M.R., Cole, S., Olmstead, R., et al., 2019. Moderators for depressed mood and systemic and transcriptional inflammatory responses: a randomized controlled trial of endotoxin. Neuropsychopharmacology 44 (3), 635–641. https://doi.org/10.1038/s41386-018-0259-6.

Kroenke, K., Spitzer, R.L., Williams, J.B.W., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Kuhlman, K.R., Robles, T.F., Dooley, L.N., Boyle, C.C., Haydon, M.D., Bower, J.E., 2018. Within-subject associations between inflammation and features of depression: using the flu vaccine as a mild inflammatory stimulus. Brain Behav. Immun. 69, 540–547. https://doi.org/10.1016/J.BBI.2018.02.001.

Kuhlman, K.R., Robles, T.F., Haydon, M.D., Dooley, L., Boyle, C.C., Bower, J.E., 2019. Early life stress sensitizes individuals to the psychological correlates of mild fluctuations in inflammation. Dev. Psychobiol. 21908 https://doi.org/10.1002/dev.21908. September.

McDade, T.W., Borja, J.B., Kuzawa, C.W., Perez, T.L.L., Adair, L.S., 2015. C-reactive protein response to influenza vaccination as a model of mild inflammatory stimulation in the Philippines. Vaccine 33 (17), 2004–2008. https://doi.org/10.1016/J.VACCINE.2015.03.019.

Morin, C.M., Belleville, G., Bélanger, L., Ivers, H., 2011. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 34 (5), 601–608. https://doi.org/10.1093/sleep/34.5.601.

Posthouwer, D., Voorbij, H.A.M., Grobbee, D.E., Numans, M.E., Van Der Bom, J.G., 2004. Influenza and pneumococcal vaccination as a model to assess C-reactive protein response to mild inflammation. Vaccine 23 (3), 362–365. https://doi.org/10.1016/j.vaccine.2004.05.035.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166 (10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092.

Steptoe, A., Hamer, M., Chida, Y., 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav. Immun. 21 (7), 901–912. https://doi.org/10.1016/j.bbi.2007.03.011.

Tsai, M.Y., Hanson, N.Q., Straka, R.J., et al., 2005a. Effect of influenza vaccine on markers of inflammation and lipid profile. J. Lab. Clin. Med. 145 (6), 323–327. https://doi.org/10.1016/J.LAB.2005.03.009.

Tsai, M.Y., Hanson, N.Q., Straka, R.J., et al., 2005b. Effect of influenza vaccine on markers of inflammation and lipid profile. J. Lab. Clin. Med. 145 (6), 323–327. https://doi.org/10.1016/j.lab.2005.03.009.