ПРОГНОЗИРОВАНИЕ ИСХОДА ВАКЦИНАЦИИ ПРОТИВ КОРИ У МЕДИЦИНСКИХ РАБОТНИКОВ

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Резюме. Проведение своевременной вакцинации является единственным гарантом элиминации коревой инфекции. По данным литературы риск заражения корью у медицинских работников в 13-19 раз выше, чем у населения в целом. Доля лиц, не сформировавших иммунный ответ на вакцинацию, может достигать 10%. Накопление серонегативных лиц в популяции может привести к вспышке коревой инфекции. Целью данной работы является поиск биохимических и иммунологических сывороточных маркеров-предикторов выработки поствакцинальных противокоревых IgG у медицинских работников. В исследовании приняли участие 76 медицинских работников в возрасте от 19 до 51 года с лабораторно подтвержденным отсутствием антител против вируса кори. Данные лица были дважды вакцинированы живой коревой вакциной (НПО «Микроген», Россия) с интервалом в 3 месяца. Определение IgG к вирусу кори, суммарных IgG, IgM, IgA, IFNγ, IL-6, С-реактивного белка, общего белка, АЛТ, АСТ, общего билирубина, мочевины, креатинина, белковых фракций проводили до вакцинации, через 1 месяц после вакцинации, через 1 месяц после ревакцинации, а также через 1 год после ревакцинации. Для оценки диагностической эффективности применения данных количественных показателей сыворотки крови при прогнозировании результата вакцинации использовался метод ROC-анализа. Разработка прогностической модели вероятности исхода вакцинации проводилась с использованием логистической регрессии. Потенциальными лабораторными предикторами вакцинальных неудач при вакцинации против кори у медицинских работников могут выступать IFNγ, суммарные IgG, IgM, общий билирубин, АЛТ на различных стадиях иммунизации. При этом наиболее информативным является определение содержания показателей IFNγ до вакцинации и IgG к вирусу кори после первой вакцинации. На основании данных показателей удалось создать регрессионные модели, предсказывающие риск как первичных, так и вторичных вакцинальных неудач. Полученные модели легли в основу разработки алгоритма прогнозирования вакцинальных неудач у медицинских работников при вакцинации против вируса кори, который может быть использован для выявления лиц из групп риска по несформированному специфическому гуморальному иммунитету. Таким образом, данный алгоритм в первую очередь ориентирован на поиск лиц, не ответивших на противокоревую вакцинацию, среди которых также можно обнаружить лиц с иммунодефицитами. Мы не

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Образец цитирования:

А.А. Ерещенко, О.А. Гусякова, Н.Б. Мигачева, Ф.Н. Гильмиярова, А.В. Лямин «Прогнозирование исхода вакцинации против кори у медицинских работников» // Медицинская иммунология, 2023. Т. 25, № 2. С. 367-376. doi: 10.15789/1563-0625-OPO-2546

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For citation:

A.A. Ereshchenko, O.A. Gusyakova, N.B. Migacheva, F.N. Gilmiyarova, A.V. Lyamin "Outcome prediction of the measles vaccination in healthcare employees", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2023, Vol. 25, no. 2, pp. 367-376.
doi: 10.15789/1563-0625-OPO-2546

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DOI: 10.15789/1563-0625-OPO-2546

исключаем, что на основании выявленных потенциальных предикторов эффективности противокоревой вакцинации возможно построение прогностических моделей и для других вакциноуправляемых инфекций.

Ключевые слова: вакцинация, корь, медицинские работники, предикторы, антитела, вакцинальная неудача

OUTCOME PREDICTION OF THE MEASLES VACCINATION IN HEALTHCARE EMPLOYEES

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Abstract. Vaccination is the only guarantee for elimination of measles infection. Healthcare workers have a 13- to 19-fold higher risk for contracting measles than the general population. The number of individuals in the population who did not respond to vaccination is up to 10%, and their accumulation may lead to an outbreak of the infection. The aim of our research was to find potential predictors of arising post-vaccination measles antibodies in the panel of biochemical and immunological serum markers in healthcare workers. The group of healthcare workers (n = 76) aged from 19 to 51 years, with proven absence of pre-existing anti-measles antibodies were twice vaccinated 3 months apart with live measles culture vaccine (SPA "Microgen", Russia). Measles-specific IgG, total IgG, IgM, IgA, IFNγ, IL-6, CRP, total protein, ALT, AST, total bilirubin, urea, creatinine, protein fractions were determined before vaccination, 1 month after vaccination, 1 month following revaccination, 1 year after revaccination. ROC analysis was used to gain access to the diagnostic performance of quantitative variables in predicting a categorical outcome. Development of a predictive probability model for the binary outcome was carried out using logistic regression. IFNγ, total IgG, IgM, total bilirubin, ALT activity at various post-immunization stages may be considered potential laboratory predictors of measles vaccination failures in healthcare workers. Meanwhile, the contents of pre-vaccination IFNγ, and IgG to measles virus after first vaccination proved to be most informative indexes, which formed the basis for the development of regression models predicting the risk of both primary and secondary vaccination failures. These models allowed to develop algorithm for predicting failures of the measles vaccination in healthcare workers that can be used for detection of persons at risk for non-forming specific humoral immunity. This algorithm is primarily focused on search for the persons who have not responded to measles vaccination, including subjects with probable immunodeficiency conditions. We do not exclude that, on the basis of revealed predictors following measles vaccination, it would be possible to build prognostic models of vaccination efficiency for other vaccine-managed infections.

Keywords: vaccination, measles, healthcare staff, predictors, antibodies, vaccination failure

Introduction

According to the World Health Organization in 2019, there was a sharp increase in measles rates worldwide, reaching the highest level in 23 years, and measles deaths worldwide increased by almost 50%. In the WHO European Region in 2019, in Ukraine, Georgia, North Macedonia, Kazakhstan, measles incidence rates exceeded 700 cases per 1 million population [17]. Several regions have lost the status of "free of endemic measles", others have failed to achieve the required measles vaccination coverage (90%) [19, 21].

Despite the fact that in 2020 the number of recorded cases of measles infection decreased, the redistribution of medical forces and funds to combat the pandemic of the new coronavirus infection led to failures in the implementation of planned vaccination – the only guarantor of the elimination of measles infection. As of November 2020, more than 94 million were not vaccinated on time due to shortage of vaccine because of the suspension of measles campaigns in 26 countries. Only isolated countries were able to resume vaccination campaigns after initial delays [20].

Within the framework of the WHO measles and rubella initiative, seven strategic priorities have been developed in the strategic framework for measles and rubella control for 2021-2030. The solution of which is inextricably linked to the activities of laboratory

services. One of them is to conduct research that contributes to achieving a high level of population immunity to measles [18]. One of the ways to solve this problem is to study post-vaccination measles humoral immunity in various professional, age, ethnic groups, as well as to identify the links of the vaccination response with the genetic, biochemical, immunological features of the body, and to search for predictors of the formation of immunity.

The aim: finding predictors of production of post-vaccination measles antibodies among biochemical and immunological serum markers in healthcare workers.

Materials and methods

Participants and design

This study approved by the Committee on Bioethics in Samara state medical university. The group of healthcare workers (n = 76), conditionally healthy between the ages of 19 and 51. Inclusion criteria were practically healthy persons with serologically confirmed absence of anti-measles antibodies. The exclusion criteria were acute chronic diseases, the presence of socially significant infections, oncological, autoimmune, allergic, rheumatological diseases, immunodeficiency, pregnancy, contraindications to measles vaccination, contact with a measles patient during the last month. These persons were twice vaccinated 3 months apart with live measles culture vaccine (SPA "Microgen", Russia). Determinations of measles IgG, total IgG, IgM, IgA, IFNγ, IL-6, CRP, total protein, ALT, AST, total bilirubin, urea, creatinine, protein fractions were carried out before vaccination (before V), 1 month after vaccination (after V1), 1 month after revaccination (after V2), 1 year after revaccination. At each study control point, all vaccinated individuals were divided into the seropositive and seronegative groups depending on the results of measles IgG determination.

Laboratory research

Biochemical and immunological parameters were determined in serum samples taken on an empty stomach. Determination of measles IgG, IFNγ, IL-6 was performed by ELISA (Vector-Best, Russia). Measurement of total IgG, IgM, IgA, CRP, total protein, ALT, AST, total bilirubin, urea, creatinine was performed by automatic biochemical analyzer Cobas Integra 400 plus (Roche-Diagnostics, Switzerland). Protein fractions were determined using capillary electrophoresis (Sebia, France).

Statistics

Statistical analysis was performed using StatTech v. 2.8.5 (Developer – StatTech LLC, Russia). Quantitative variables were assessed for normality using the Shapiro-Wilk test (when the number of subjects was less than 50) or the Kolmogorov-Smirnov test (when the number of subjects was more than 50). Quantitative variables following non normal distribution were described using median (Me) and lower and upper quartiles ($Q_{0.25}$-$Q_{0.75}$). Mann–Whitney U test was used to compare two groups on a quantitative variable whose distribution differed from the normal distribution. Statistical significance was assumed at $p < 0.05$. ROC analysis was used to assess the diagnostic performance of quantitative variables in predicting a categorical outcome. The presence or absence of measles IgG is selected as a dependent binary variable. The optimal cut-off value of the quantitative variable at was estimated using the Youden's J statistic. The development of a prognostic model for the probability of a binary outcome was carried out using logistic regression. Nagelkerke R was used as a measure of the model performance.

Results

Prediction of primary vaccination failures

The analyzed substances representing statistically significant differences between the seropositive and seronegative groups in early (1 month after revaccination) and late (1 year) post-vaccination period, were considered as potential predictors of the absence of measles post-vaccination humoral immunity. At 1 month after vaccination, statistical differences for the groups of responders and non-responders were identified by the following analytes: IFNγ, total IgG, IgM, measles IgG, total bilirubin, ALT at various stages of immunization (Table 1).

The diagnostic performance of the tests was evaluated by ROC analysis and is presented in Table 2.

Thus, these markers can be considered as additional predictors of primary vaccination failures in measles vaccination in healthcare workers.

To analyze the relationship of these analyzed substances with the absence of immune response formation, a logistic regression method with logit transformation of the obtained model was used. Regression equations was compiled, including combination of these analytical data from which a model characterized by a higher quality predictive test was selected:

$P = 1/(1+e^{-z})\ 100\%$

$z = 5.773\text{-}1.5X_{IFN\gamma\ before\ V}+3.173X_{Measles\ IgG\ after\ V1,}$

where P – probability of immune response to vaccination, e – exponent (e = 2.7182 – constant), z – dependent binary variable (response and non-response to vaccination), $X_{IFN\gamma\ before\ V}$ – serum concentration IFNγ before V, $X_{Measles\ IgG\ after\ V1}$ – serum concentration Measles IgG after V1.

The resulting regression model is statistically significant ($p < 0.001$). Based on the value of Nagelkerke R , the model explains 59.6% of the observed response in early post-vaccination period variance. 1 pg/ml increase of IFNγ before V is associated with 3.8 times decrease in availability of

TABLE 1. STATISTICAL DIFFERENCES IN SERUM BIOCHEMICAL AND IMMUNOLOGICAL PARAMETERS DEPENDING ON THE RESPONSE TO VACCINATION IN EARLY POST-VACCINATION PERIOD (ONLY STATISTICALLY RELEVANT DATA ARE PRESENTED)

Analytes	Categories non-responders (n = 6) responders (n = 70)	Me	$Q_{0.25}$-$Q_{0.75}$	p
IFNγ before V, pg/mL	non-responders	4.81	3.82-5.80	0.002*
	responders	3.77	3.54-3.99	
Total IgG before V, g/L	non-responders	6.38	5.93-7.80	0.032*
	responders	8.13	6.80-9.52	
Measles IgG after V1, IU/m	non-responders	0.39	0.24-0.58	< 0.001*
	responders	1.71	0.92-1.96	
ALT after V1, U/L	non-responders	21.9	10.9-32.9	0.026*
	responders	11.2	5.5-17.0	
Total bilirubin after V1, μmol/L	non-responders	8.8	4.8-12.7	0.005*
	responders	4.1	2.8-5.5	

Note. *, differences are statistically significant (p < 0.05).

TABLE 2. DIAGNOSTIC ABILITY OF LABORATORY PARAMETERS AS MARKERS OF VACCINATION FAILURES IN THE EARLY POST-VACCINATION PERIOD

Analytes	AUC (p)	Se, %	Sp, %	Cut-off
IFNγ before V, pg/mL	0.744 (p = 0.01*)	68.8	81.8	> 4.29
Total IgG before V, g/L	0.703 (p = 0.032*)	65.1	72.2	< 7.5
Measles IgG after V1, IU/mL	0.893 (p < 0.001*)	87.5	90.9	< 0.702
ALT after V1, U/L	0.917 (p = 0.033*)	83.3	50.0	> 14.4
Total bilirubin after V1, μmol/L	0.958 (p = 0.019*)	83.3	75.0	> 6.3

Note. *, model is statistically significant (p < 0.05).

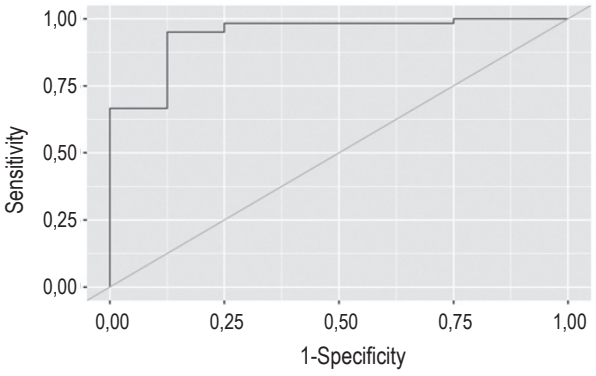

Figure 1. ROC-curve characterizing the dependence of the probability response to vaccination in early post-vaccination period on value of logistic function P

a response to vaccination in early post-vaccination period odds. 1 IU/ml increase of measles IgG after V1 is associated with 33.876 times increase in response on vaccination in early post-vaccination period odds.

When evaluating the dependence of the probability of response on vaccination in early post-vaccination period on the value of logistic function P using the ROC analysis, the following curve was obtained (Figure 1).

The area under the ROC curve comprised 0.944±0.029 with 95% CI: 0.887-1.000. The resulting model was statistically significant (p < 0.001). The cut-off value of logistic function P which corresponds to the highest Youden's J statistic is 0.64. If logistic function P was greater than or equal to this value availability of a response to vaccination in early post-

vaccination period was predicted. The sensitivity and specificity of the method were 95.0% and 87.5%, respectively.

Prediction of secondary vaccination failures

1 year after vaccination, statistical differences for the groups of responders and non-responders were identified by the following analytes: IFNγ, total IgM, measles IgG at various stages of immunization (Table 3).

To predict secondary vaccination failures, in addition to specific IgG, indicators of total IgM in the pre-vaccination period and after the first vaccination, as well as IFNγ before vaccination can be used (Table 4).

The compounded regression model again was based IFNγ before V and measles IgG after V1:

$P = 1/(1+e^{-z})\ 100\%$

$z = 1.384\text{-}0.822X_{IFN\gamma\ before\ V}+2.494X_{Measles\ IgG\ after\ V1}$

where P – probability of immune response to vaccination, e – exponent (e = 2.7182 – constant), z – dependent binary variable (response and non-response to vaccination), $X_{IFN\gamma\ before\ V}$ – serum concentration IFNγ before V, $X_{Measles\ IgG\ after\ V1}$ – serum concentration Measles IgG after V1.

The resulting regression model is statistically significant (p=0.001). Based on the value of Nagelkerke R^2, the model explains 53.9% of the observed response in early post-vaccination period variance. Based

TABLE 3. STATISTICAL DIFFERENCES IN SERUM BIOCHEMICAL AND IMMUNOLOGICAL PARAMETERS DEPENDING ON THE RESPONSE TO VACCINATION IN EARLY POST-VACCINATION PERIOD (ONLY STATISTICALLY RELEVANT DATA ARE PRESENTED)

Analytes	Categories non-responders (n = 6) responders (n = 65)	Me	$Q_{0.25}$-$Q_{0.75}$	p
Total IgM before V, g/L	non-responders	1.18	0.98-2.12	0.045*
	responders	0.99	0.71-1.22	
Total IgM after V1, g/L	non-responders	1.46	1.09-2.77	0.025*
	responders	1.04	0.76-1.38	
Measles IgG after V1, IU/mL	non-responders	0.531	0.368-1.539	0.035*
	responders	1.690	0.827-1.915	
Measles IgG after V2, IU/mL	non-responders	0.649	0.450-0.848	< 0.001*
	responders	1.467	1.193-1.742	
IFNγ before V, pg/mL	non-responders	4.39	3.14-5.63	0.045*
	responders	3.41	3.21-4.00	

Note. *, differences are statistically significant (p < 0.05).

TABLE 4. DIAGNOSTIC CAPACITY OF LABORATORY INDICATORS AS MARKERS OF SECONDARY VACCINATION FAILURES IN MEASLES VACCINATION

Analytes	AUC (p)	Se, %	Sp, %	Cut-off
Total IgM before V, g/L	0.722 (p = 0.045*)	63.2	54.5	> 1.18
Total IgM after V1, g/L	0.758 (p = 0.025*)	89.5	50.0	> 1.76
Measles IgG after V1, IU/mL	0.737 (p = 0.035*)	94.4	54.4	< 0.549
Measles IgG after V2, IU/mL	0.960 (p < 0.001*)	100.0	90.0	< 0.829
IFNγ before V, pg/mL	0.765 (p < 0.023*)	71.1	74.7	> 3.88

Note. *, model is statistically significant (p < 0.05).

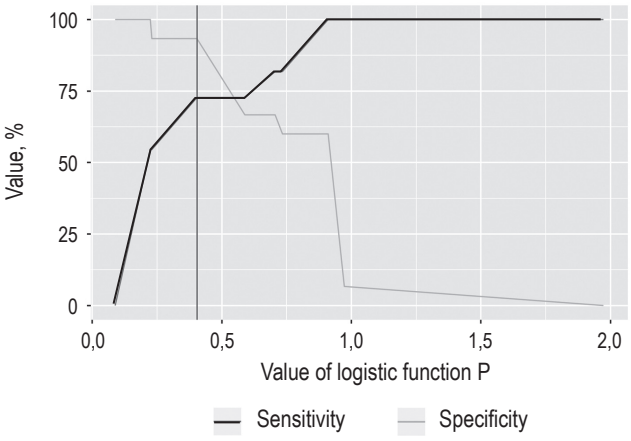

Figure 2. Analysis of the sensitivity and specificity of regression model depending on value of logistic function P

on the values of the regression coefficients, a direct relationship was established between IgG measles after V1, and the inverse association IFNγ before V with the probability of response to vaccine in 1 year after vaccination (Table 5).

When evaluating the dependence of the probability of response on vaccination in 1-year post-vaccination period on the value of logistic function P using the ROC analysis, the following results was obtained (Figure 2).

The area under the ROC curve comprised 0.885±0.066 with 95% CI: 0.755-1.000. The resulting model was statistically significant ($p < 0.001$). The cut-off value of logistic function P which corresponds to the highest Youden's J statistic is 0.4. The sensitivity and specificity of the method were 93.3% and 72.7%, respectively.

TABLE 5. CHARACTERISTICS OF THE ASSOCIATION OF PREDICTORS WITH THE PROBABILITY OF RESPONSE TO MEASLES VACCINE IN 1 YEAR AFTER VACCINATION

Predictors	Unadjusted		Adjusted	
	COR; 95% CI	p	AOR; 95% CI	p
IFNγ before V	0.561; 0.264-1.192	0.133	0.440; 0.196-0.988	0.047*
Measles IgG after V1	7.306; 1.493-35.766	0.014*	12.107; 1.709-85.798	0.013*

Note. *, association of the outcome value with the predictor value is statistically significant ($p < 0.05$).

Discussion

Based on the data obtained, "Algorithm for predicting vaccination failures in healthcare professionals during vaccination to measles virus" was developed (Figure 3), designed for use by a therapist and immunologist during planned and emergency preventive measures.

The algorithm is implemented as follows:

1) Prior to measles vaccination, laboratory determination of IFNγ should be carried out as well as measurement of measles IgG 1 month after the first vaccination.

2) Prediction of risk of primary vaccination failures. Apply the model to predict the risk of primary vaccination failures. If an appropriate risk is detected, decide on the need to use additional immunocorrection agents during revaccination. It is also necessary to control measles IgG 1 month after revaccination. In the absence of antibodies, repeat the control after 1 year. If antibodies are also not detected after a year, the case is classified as an initial vaccination failure. Consultation of immunologist is recommended. If measles IgG 1 month after revaccination are detected, assess the risk of secondary vaccination failure.

3) Prediction of risk of secondary vaccination failures. In a favorable prediction or unconfirmed risk of primary vaccination failures, apply a model to predict the risk of secondary vaccination failures. If an appropriate risk is detected, control measles IgG after 1 year. If antibodies are not detected, the case is classified as a secondary vaccination failure. Consultation of immunologist is also recommended.

4) In the absence of a predicted risk of primary and secondary vaccination failures, it is recommended to carry out planned revaccination.

This algorithm allows reduce the workload on the laboratory during serocontrol and to detect persons from risk groups due to the lack of immunity formation and take them under control.

Thus, IFNγ before V and measles IgG after V1 rates demonstrated high diagnostic value in the early prediction of both primary (1 month after revaccination) and secondary (1 year after revaccination) vaccination failures. Based on resulting regression model, it is possible to identify a risk group for the formation of primary vaccination failure after the first vaccination. Which makes it possible, if it is necessary, to use additional methods and means of immunocorrection. Such as administering a booster dose, thereby increasing the likelihood of the final formation of post-vaccination humoral immunity.

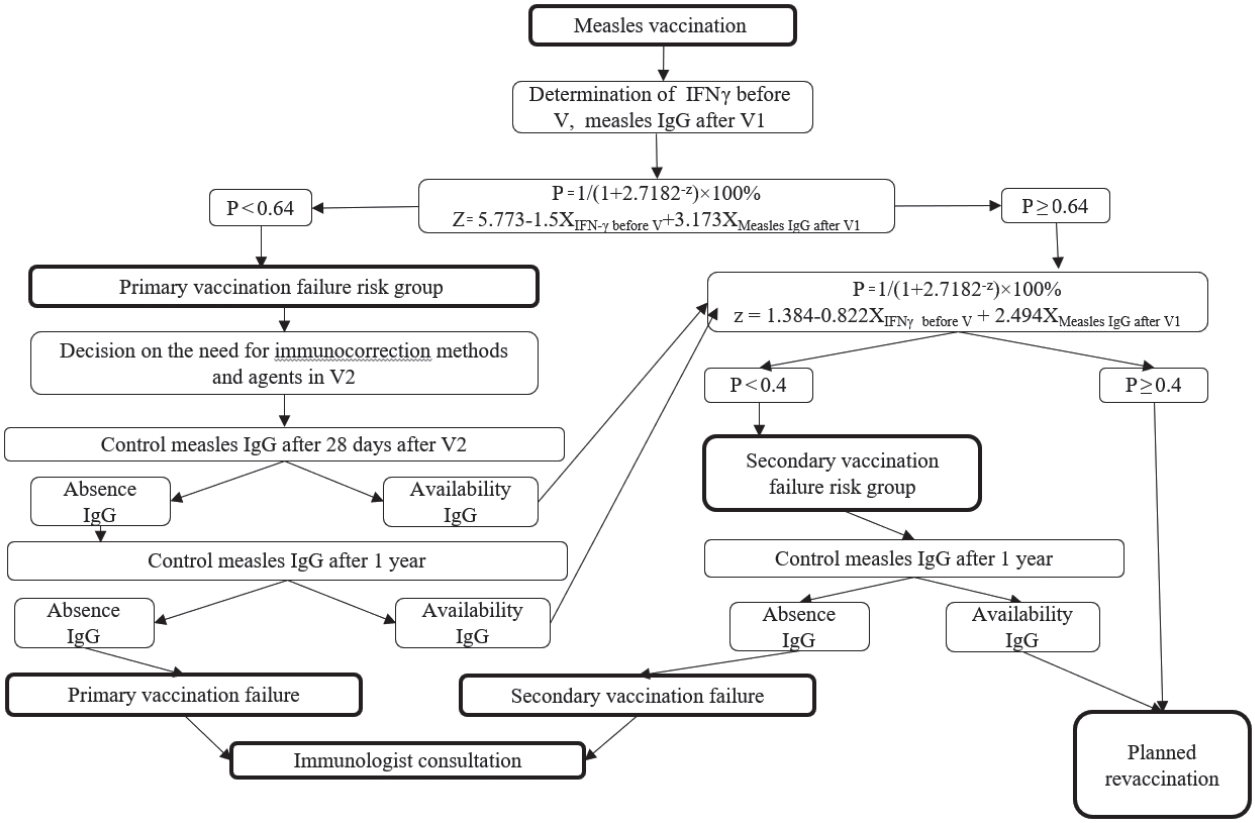

Figure 3. Algorithm for predicting vaccination failures in healthcare workers during vaccination to measles virus

Regarding studies on the effectiveness of measles vaccination, there are works on the prediction of a specific humoral immune response based on the initial parameters of the immune status of children vaccinated against measles, rubella and mumps by mathematical modeling. It is interesting to note that in these researches the IFNγ also became one of the predictors for the successful response on vaccination 1 month after vaccination for rubella viruses and mumps. For the measles virus, this parameter turned out to be less informative. However, the study, as well as our work, established negative correlation associations of pre-vaccination IFNγ blood content with specific IgG counts at 1 month and 1 year after measles vaccination [14, 15].

The number of individuals in the population who did not respond to vaccination can be 2-12% [4], their accumulation can lead to an outbreak of infection, especially one as highly contagious as measles [11]. According to literature, healthcare workers have a 13-19 times higher risk of contracting measles than the general population [1, 12]. The lack of post-vaccination immunity is a risk factor for healthcare workers (infection can occur through infected patients, including in the prodromal period). On the other hand, susceptible healthcare workers can become a source of infection and put their colleagues/patients at risk. [6]. According to regulatory documents, in case of refusal to vaccinate, a worker can be removed from his professional duties [3]. In a number of countries adapt a mandatory vaccination policy with dismissal for offers [2]. At the same time, the actions of the employer when identifying a person who did not respond to vaccination are not regulated in any way. One of the options for solving this problem may be a more thorough testing of such persons, including with laboratory determination of specific IgA or cellular post-vaccination measles immunity markers.

In our other studies, it was found that after immunization, the number of seropositive to the measles virus persons decreases by 7% over a three-year period (data are not presented in this article). At the moment, laboratory monitoring of measles IgG in healthcare professionals is not carried out either as part of annual medical examinations or as part of delayed sero-monitoring of vaccination effectiveness (after 1 year or more). If monitoring of the production of measles antibodies is carried out, then as a rule, once, on average, 1-2 months after the vaccination course. Immunized individuals are not examined

until the next planned revaccination, which is carried out only after 10 years. Such tactics potentially lead to the skipping of secondary vaccination failures and the accumulation in the population of persons who do not have humoral immunity to the measles virus. The prognostic models we obtained demonstrated high quality diagnostic test according to the expert scale Hosmer N.T. Based on only two laboratory parameters, after the first vaccination, it is possible to detect persons from risk groups both for primary and secondary vaccination failures. Thus, it is possible to significantly reduce economic costs when controlling delayed vaccination results.

Current research focuses mainly on finding genetic predictors of vaccine reactivity and efficacy. Genetic determinants of the neutralizing antibody response induced by the measles vaccine (e.g., genetic variants of CD46 and IFI44L (Interferon induced protein 44 like), other genetic markers) are under research [5, 9]. It can prospectively identify potential non-responders and susceptible individuals who will ultimately require additional measles vaccination or the use of an improved vaccine. But unfortunately, at the moment, it is impossible to conduct widespread genetic research due to their labor intensity and high cost. However, not only genetic, but also immunological, biochemical, hematological markers or their combination in a mathematical model can act as predictors of vaccination effectiveness [7, 10, 13, 16]. Their determination in the blood seems less laborious and costly, which means that it makes the prognosis of the outcome with their help more accessible.

Since healthy medical professionals were subject to examination, almost all values of the studied indicators fit into the reference intervals. Nevertheless, cases of primary and secondary vaccination failures were identified among the examined persons. These failures may have been both specific for measles vaccination (genetic features) and immunodeficiency conditions. The proposed algorithm allows to detect persons from both of these groups. Thus, this algorithm is primarily focused on finding persons who have not responded to measles vaccination, among whom immunodeficiency persons can also be found. We do not exclude that based on the identified potential predictors of the effectiveness of measles vaccination, it is possible to build prognostic models for other vaccine-managed infections. This area is a prospect of our research.

It is known that medical professionals are characterized by certain features of immune status [8]. Our prediction model is constructed in the study of post-vaccination immunity of healthcare workers; however, it cannot be ruled out that it may be applicable to the population as a whole. The study of the predictive ability of the obtained models for representatives of other professions and for the adult population as a whole is also one of the prospects for this work.

Conclusions

Potential laboratory predictors of vaccination failures in measles vaccination in healthcare workers may considered IFNγ, total IgG, IgM, total bilirubin, activity ALT at various stages of immunization. At the same time, the most informative is the determination of the content of pre-vaccination IFNγ and IgG to measles virus after first vaccination, which formed the basis for the development of regression models predicting the risk of both primary and secondary vaccination failures. These models formed the basis of the algorithm for predicting vaccination failures in healthcare workers during vaccination to measles virus that can be used for detection of persons from risk groups for non-formed specific humoral immunity.

Acknowledgments

Authors would like to thank Vladimir Alexandrovich Antipov, assistant of the chair of fundamental and clinical biochemistry with laboratory diagnostics of SamSMU, for his help in preparing English version of the article.

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Поступила 09.07.2022
Отправлена на доработку 20.08.2022
Принята к печати 10.09.2022

Received 09.07.2022
Revision received 20.08.2022
Accepted 10.09.2022