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Prediction of Multiple Peptide Based Vaccine from E1, E2 and Capsid Proteins of Rubella Virus: An *In-Silico* Approach

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Abstract

Rubella is a single strand RNA virus in structure that belongs to *Togaviridae* family. It causes rubella by respiratory droplet transmission and congenital rubella syndrome if infection to the mother occurs during pregnancy. The current life attenuated vaccine is given as part of MMR vaccine. It has many side effects and contraindicated in pregnancy and immunosuppressed persons. The aim of this study is to determine antigenic peptides from E1, E2, and Capsid proteins that can be used for multiple peptide vaccine design using *In-Silico* study. A total of 189 sequences of three proteins were obtained from NCBI and subjected to multiple sequence alignments using CLUSTALW tool to determine conserved regions.

Immune Epitope Data Base tools were used to determine B cell epitopes, these tools are Bepipred Linear B cell epitopes prediction, surface accessibility and antigenicity prediction. Epitope binding to MHC class I and class II and their population coverage were also determined using IEDB software. The analysis results are as follow, for B cell binding from E1 were (PVCQRHSP, QYHPTAC, and QVPPD), from E2 (AQYPP, PAHP and TTAANSTTAATPATA), and (PPPP, PPQQPQPP and PPHT) from capsid protein. All these peptides have high score in Linear B cell epitopes prediction, surface accessibility and antigenicity prediction. On another hand peptides that reacted to MHC class I were (YFNPGGSYY, **FVLLVPWV**L and FTNLGTPPL) form E1, E2 and capsid protein respectively. It worth noting that the peptide **FVLLVPWV**L from E2 protein is also binds to MHC class II with high affinity. All T cell peptides had highest population coverage, and the combined coverage for all peptides in this study was found to be 100%. Using *In-Silico* studies will ensure less risk of virulence and side effects. Evaluation of antibodies response in animal models is needed to confirm efficacy of these epitopes in inducing protective immune response.

Keywords: Epitope; Immune epitope data base IEDB; *In-silico*; Peptide vaccine; Rubella

Introduction

Rubella virus is a positive sense single strand RNA virus that belongs to *Rubivirus* genus of the *Togaviridae* family, it contains 9.7 KB genome which surrounded by capsid protein (nucleocapsid protein). The nucleocapsids surrounded by envelop that contains E1 and E2 glycoproteins, these proteins arranged in parallel rows on the outer surface, giving the virion different shapes [1-3]. Rubella virus is classified into two clades, clade 1 and clade 2 according to E1 protein, and they are divided further into 11 genotype (1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, 1J, 2A, 2B) and 1 provisional genotype [4-6]. After outbreak that occurred in 1964 in USA and Europe which affected about 1% of pregnancies, rubella infection was studied more [7]. Worldwide there are more than 100000 babies affected by congenital rubella syndrome each year, and there were more than 800000 rubella cases reports in 1999 and 2001 with majority of cases reported by Russian federation [8]. Rubella is highly infectious disease transmitted by respiratory droplet, usually causes mild disease in children with symptoms of low grade fever, maculopapular rash, arthralgia and myalgia [9-11]. However infection of women during pregnancy especially in first 12 weeks may cause death of fetus or Congenital Rubella Syndrome which has different clinical manifestations such as sensory neural deafness, congenital cataract and glaucoma, microcephaly and heart disease that occur in 80%-90% of cases [9,10].The immune response in human body developed after vaccination and infection, with formation of antibodies against structural protein [12-15], which directed mainly toward E1, E2 and capsid protein. The antibodies against E1 glycoprotein persist for long time, in contrast, the antibodies against E2 and capsid protein tend to persist for short time, and this is may be due to the difference in accessibility by immune system [2,5,16-19].

The current live attenuated vaccine is Rubella vaccine RA 27/3 (human diploid fibroblast) strain which used in combined with mumps and measles vaccine (MMR) and effectively reduce disease incidence [20-23]. However, the vaccine has some side effects such as joint symptoms that may occur in up to 60% of post pubertal female but does not cause chronic joint disease, also lymphadenopathy, rash and allergy [24-26]. In fact, it is contraindicated in immunosuppression, malignant disease, and during pregnancy because of its risk to the fetus, but there was no confirmation of congenital rubella syndrome in babies of pregnant women who took the vaccine [10, 27-29]. Because of significant effects of rubella on people health, a safe vaccine with maximum efficacy, good coverage and least side effects is needed,

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especially for immunosuppressed patients and pregnant women due to high disease burden. Thus the aim of this study was to determine antigenic peptides from E1, E2 and Capsid proteins that can be used for multiple peptide based vaccine design against rubella virus using immunoinformatics analysis. This study is unique in rubella virus vaccine design because it deals with three structural proteins that can induce protective immune response, in order to cover most possibilities of epitopes that can be used as vaccine to achieves maximum results, Unlike other type of vaccine, using *In-Silico* studies to identify epitopes will insure less risk of virulence and side effects that can be seen with lives attenuated vaccine [30], as only specific epitope will be used, it also allow production of vaccine with chemical safety, low cost and good population coverage as only conserved epitopes are tested.

In-Silico Study Materials and Methods

A total of 183 rubella virus E1 glycoprotein sequences, four E2 glycoprotein sequences and only two capsid protein sequences were obtained from NCBI (www.ncbi.nlm.nih.gov/protein/?term=) in FASTA format in March 2017 (Table 1).

For all three proteins, reference sequences were identified from NCBI reference sequence as shown in Table 2.

All sequences of each protein were subjected to multiple sequence alignments using CLUSTALW tool of BIOEDIT sequence alignment editor (version 7.2.5.0) in order to identify conserved regions between sequences (Figure 1). Then epitopes prediction and analysis of each protein was done using different tools of immune epitope data base IEDP software (http://www.iedb.org) [31].

Epitopes Prediction

Prediction of B cell epitopes: The first step in the identification of antigenic epitopes in the pathogens is the identification of linear peptide parts. A combination between hidden Markov model (HMM) and (Parker and Levitt) method was done to predict epitopes accurately (Figure 2) [32]. Using IEDB software particularly Bepipred linear epitope prediction tool, B cell epitopes from conserved regions were identified from the E1, E2 and capsid protein with specific default threshold value for each protein, as shown in Table 3 [33].

Surface accessibility prediction: The indices of surface probability method were developed to increase confidence in provisional alignment for comparing other sequences predicted by the chou and fasman method and garnier et al. method, And this surface probability method assumes the absence of significant internal deletions or insertions [34]. Emini surface accessibility prediction tool of IEDP was used to predict surface accessibility using default threshold value for each protein as shown in Table 3 [34].

Epitopes antigenicity sites: Identification of antigenic sites for each protein with default threshold value was conducted using Kolaskar and Tongaonker antigenicity tool of IEDB as demonstrate in Table 3 [35].

MHC epitope prediction: IEDP server (http://www.iedb.org) was used through specific tools to determine MHC1 and MHC II binding epitopes. This server uses specific scoring IC50 (inhibitory concentration 50) to predict epitopes that bind to different MHC class I and MHC class II alleles.

MHC class I epitope prediction: The MHC system is an example of receptor that can interact with linear ligands of variable lengths, and the method of prediction for MHC class I affinity was been tested on

Protein	Gene bank protein accession number	Country	Region
CAPSID	NP_740662.1*	USA	North America
	AAQ55240.1	USA	North America
E2	NP_740663.1*	Japan	East Asia
	BAI22820.1	Japan	East Asia
	BAI22819.1	Japan	East Asia
	ACI02324.1	Italy	Eastern Europe
E1	NP_740664.1*	USA	North America
	BAB88324.1	Japan	East Asia
	BAB88323.1	Japan	East Asia
	BAB88322.1	Japan	East Asia
	BAB88321.1	Japan	East Asia
	BAB88320.1	Japan	East Asia
	BAB88319.1	Japan	East Asia
	BAC11764.1	Mongolia	North East Asia
	BAC11763.1	Mongolia	North East Asia
	BAC11762.1	Mongolia	North East Asia
	BAC11761.1	Mongolia	North East Asia
	BAC11760.1	Mongolia	North East Asia
	BAC10557.1	Japan	East Asia
	BAC10556.1	Japan	East Asia
	BAC10555.1	Japan	East Asia
	BAC10554.1	Japan	East Asia
	AAP74765.1	USA	North America
	AAP74764.1	USA	North America
	AAP74763.1	USA	North America
	AAP74762.1	USA	North America
	AAP74761.1	USA	North America
	AAP83127.1	USA	North America
	ABR67916.1	Russia	East Asia
	ABR67915.1	Russia	East Asia
	ABR67914.1	Russia	East Asia
	ABR67913.1	Russia	East Asia
	ABR67912.1	Russia	East Asia
	ABR67911.1	Russia	East Asia
	ABR67910.1	Russia	East Asia
	ABR67909.1	Russia	East Asia
	ABR67908.1	Russia	East Asia
	ABR67907.1	Russia	East Asia
	ABR67906.1	Russia	East Asia
	ABR67905.1	Russia	East Asia
	AAQ18152.1	Japan	East Asia
	AAQ18151.1	Japan	East Asia
	AAQ18150.1	Japan	East Asia
	AAQ18149.1	Japan	East Asia
	BAA19904.1	Japan	East Asia
	BAA19903.1	Japan	East Asia
	BAA19902.1	Japan	East Asia
	BAA19901.1	Japan	East Asia
	BAA19900.1	Japan	East Asia
	BAA19899.1	Japan	East Asia
	BAA19898.1	Japan	East Asia
	BAA19897.1	Japan	East Asia
	BAA19896.1	Japan	East Asia
	BAA19895.1	Japan	East Asia
	BAA19894.1	Japan	East Asia
	BAA19893.1	Japan	East Asia

Table 1: Countries and accession numbers of retrieved sequences from NCBI; *Ref sequence, remaining data as extra file.

large set of quantitative peptide MHC class I measurement affinity on the IEDB [36], by using artificial neutral network (ANN) method and length of nine amino acid, all conserved epitopes bound with score equal or less than 300 IC50 for all three structural proteins were chosen for further analysis [37].

MHC class II binding prediction: One of the major goals of the immunological research is the identification of MHC class II restricted peptide epitopes, and for that reason many computational tools have been developed but also their performance has lack of large scale systematic evaluation, and we use comprehensive dataset consisted from thousands of previously unpublished MHC peptide binding affinities and peptide MHC crystal structures, which all tested for

Protein	Accession number	Size
E1	NP_740664.1	481 AA
E2	NP_740663.1	282 AA
Capsid	NP_740662.1	300 AA

Table 2: Reference sequence of three proteins; AA: Amino Acid.

Protein	Linear B cell epitopes	Surface accessibility	Epitopes antigenicity
E1	0.323	1.00	1.053
E2	0.263	1.00	1.048
Capsid	0.971	1.00	0.999

Table 3: Default threshold for all three proteins used in Linear B cell epitopes prediction, surface accessibility and epitopes antigenicity prediction.

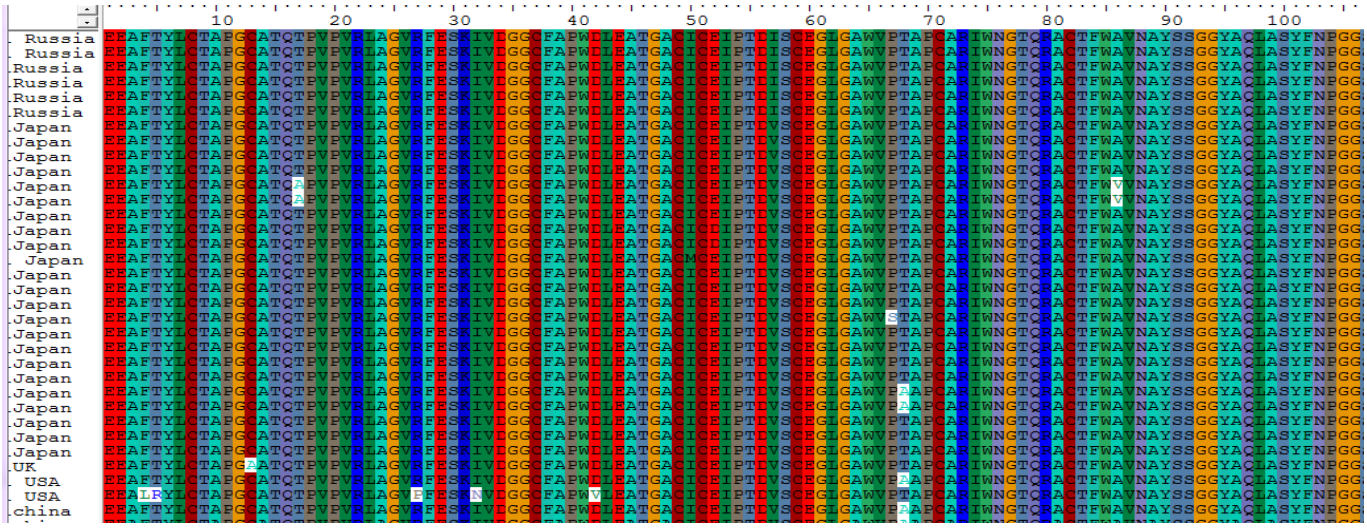

Figure 1: Multiple sequence alignment of E1 protein sequences from data base using BIOEDIT software. Uncolored regions represent mutated residues in the sequence.

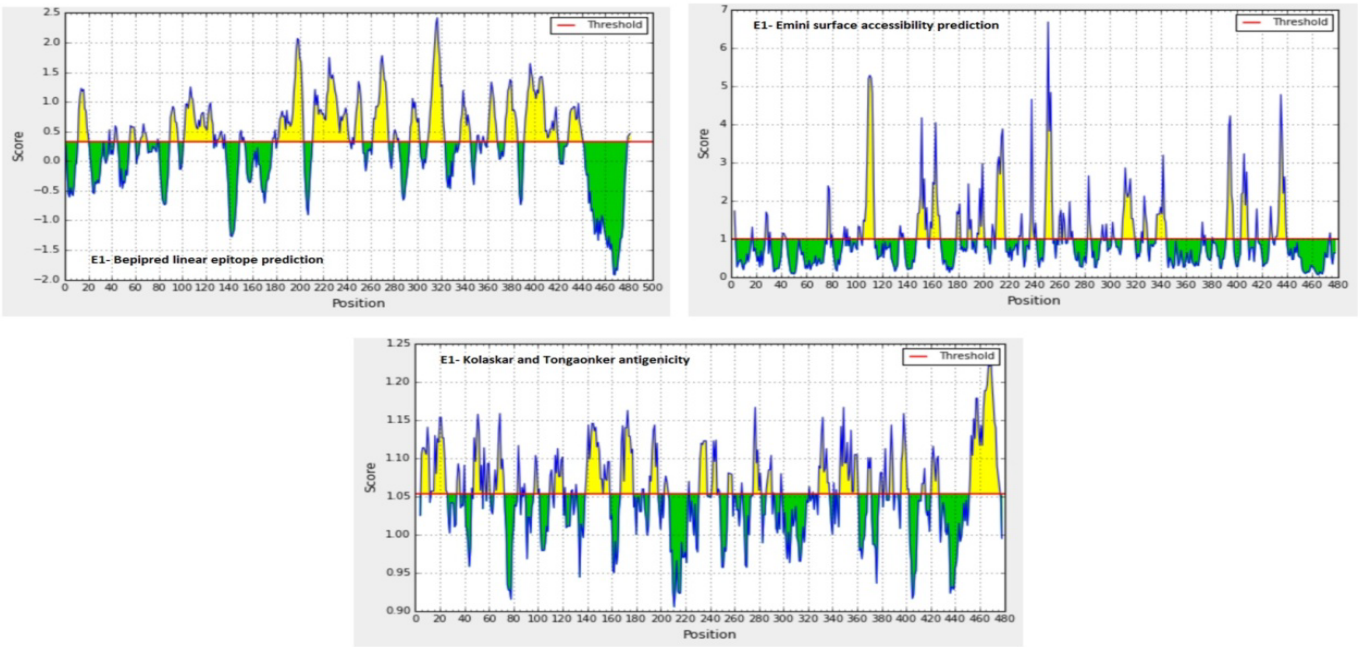

Figure 2: Prediction of B cell epitopes by various scales for E1 protein; Remaining figures as extra file.

CD4+ T cell responses to evaluate the publicly available MHC class II binding prediction tools performances [38]. Therefore MHCII binding tool from IEDP was used by applying NN align as prediction method. Then using IC50 prediction value equal or less than 1000, all conserved epitopes were chosen for more analysis [38].

Population coverage: The estimation of the population coverage are based on the MHC binding with or without T cell restriction data, there for Nemours based tool was developed to predict population coverage of T cell epitope-based diagnostic and vaccines based on MHC binding with or without T cell restriction data [39]. All alleles that interact with epitopes from E1, E2 and capsid protein were subjected population coverage tool of IEDB (http://tools.iedb.org/tools/population/iedb_input) to calculate the whole world population coverage of MHC class I, MHC II and combined MHC I and II alleles for each protein [39].

Homology modeling: The 3D structure for the three different proteins was obtained using **Raptor X** structure prediction server [40] and **Chimera** 1.8 [41] was used to demonstrate the structure of proposed B cell and T cell epitopes that can be utilized for vaccine development as shown in Figure 3.

Results

Prediction of B cell epitopes

All three proteins (E1, E2 and capsid protein) was tested using Bepipred linear epitope production, Emini surface accessibility and Kolaskar and Tongaonkar antigenicity tool of IEDB. In Bepiprd linear epitope prediction method the average binding score for E1, E2 and capsid protein were 0.32, 0.26 and 0.97 respectively, with minimum and maximum values as shown in Table 4. All values equal or greater than the default threshold were considered as potential B-cell binders.

Regarding Emini surface accessibility prediction, the average binding score of E1, E2 and capsid was 1.00, and minimum and maximum values as displayed in Table 4. All values equal or greater than the default threshold were predicted to have good surface accessibility.

All proteins were subjected to Kolaskar and Tongaonkar antigenicity prediction tool of IEDB to predict peptides with probability of being antigenic, the average threshold value for E1 was 1.05, E2 was 1.04 and 0.90 for capsid protein, with minimum and maximum values shown in Table 4. Epitopes with values equal or greater than the average score are considered as antigenic peptides.

For **E1** protein seven predicted epitopes had succeeded both antigenicity and surface accessibility test. Peptide **PVCQRHSP** from 233 to 240 was found to have high score.

Test	Protein	Average score	Minimum score	Maximum score
Bepiprd linear epitope prediction	E1	0.32	- 1.90	2.41
	E2	0.26	- 2.58	2.89
	Capsid	0.97	- 1.80	2.90
Emini surface accessibility prediction	E1	1.00	0.57	6.69
	E2	1.00	0.58	5.43
	Capsid	1.00	0.06	4.20
Antigenic peptide prediction	E1	1.05	0.90	1.23
	E2	1.04	0.90	1.22
	Capsid	0.90	0.80	1.10

Table 4: Average, minimum and maximum score values of the three tests.

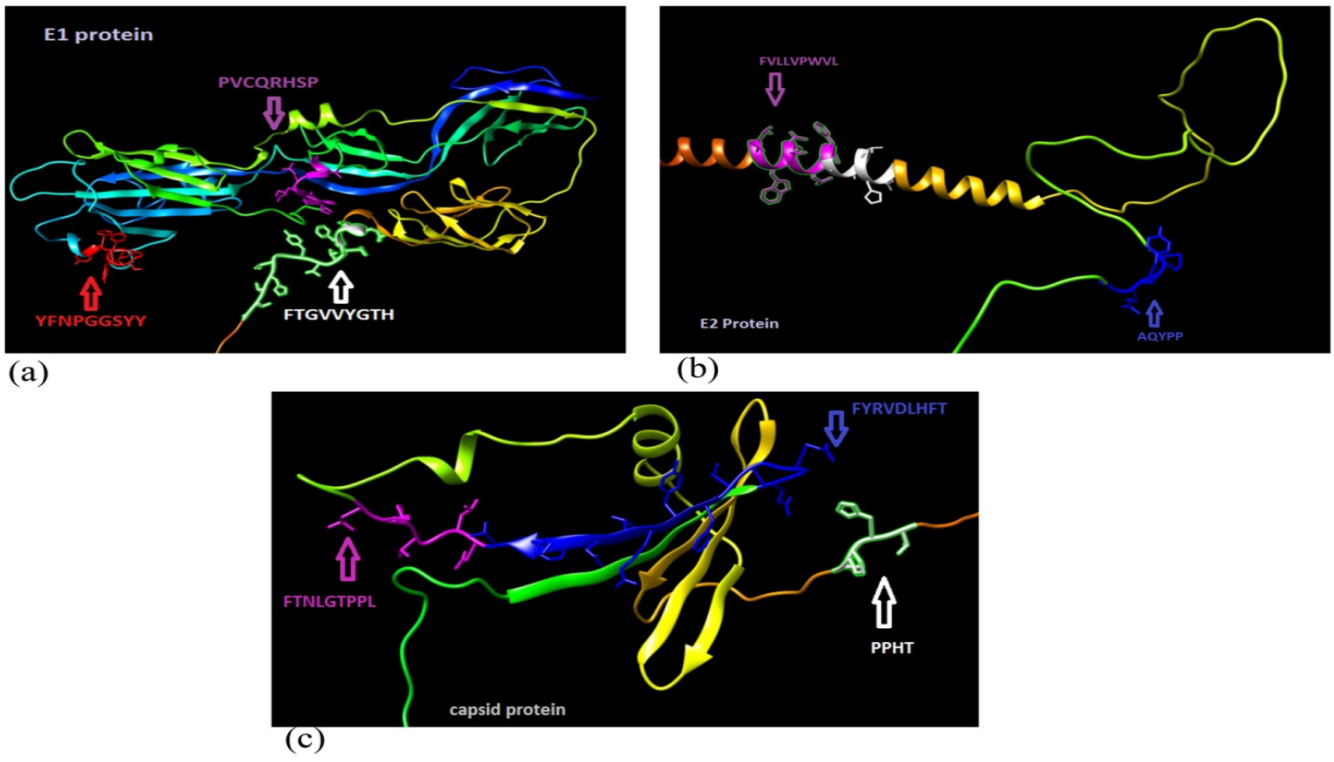

Figure 3: Proposed epitope for vaccine development; a) Proposed peptide of E1 protein that bind to B cell (magenta), MHC I (red), MHC II (white); b) Proposed peptide of E2 protein that bind to B cell (blue), MHC I (magenta), MHC II (magenta& white); c) Proposed peptide of capsid protein that bind to B cell (white), MHC I (magenta), MHC II (blue).

Protein	Bepipred Linear Epitope Prediction				Surface accessibility score	Antigenicity score
	Peptide	start	end	length		
E1	**PVCQRHSP**	233	240	8	1.167	1.116
	QYHPTAC	111	117	7	1.078	1.104
	QVPPD	195	199	5	1.831	1.078
E2	**AQYPP**	163	167	5	2.363	1.074
	PAHP	200	203	4	1.454	1.074
	TTAANSTTAATPATA	106	120	15	1.871	1.072
CAPSID	PPPP	78	81	4	1.565	1.064
	PPQQPQPP	100	107	8	3.02	1.046
	PPHT	258	261	4	1.285	1.036

Table 5: Result of predicted B cell epitopes by different tools; Remaining data as extra file.

The result of **E2** glycoprotein showed that seven peptides had passed the antigenicity prediction and surface accessibility prediction test, **AQYPP** from 163 to 167 was found to have greatest score among all other peptides in both tests.

Analysis of **Capsid** protein resulted in nine peptides that passed both tests, and **PPHT** from 258 to 261 was found to have high score in Emini surface accessibility and Kolaskar and Tongaonkar antigenicity prediction test. The result is summarized in Table 5. Various tools illustrated in Figure 2.

Prediction of T-cell epitopes and MHC class I interaction analysis

Epitopes sequences of E1, E2 and capsid subjected to MHC class I binding prediction tool of IEDP. T-cell epitope predicted to interact with different MHC class I alleles using ANN (artificial natural network) as prediction method and length of nine amino acids. Using same score for all protein of 300 IC50, 12 peptide of **E1** were found to interact with MHC class I. The peptide **YFNPGGSSY** (101-109) had height affinity to interact with the largest number of alleles (10 alleles, HLA-A*29:02, HLA-A*30:02, HLA-B*15:01, HLA-B*15:02, HLA-B*35:01, HLA-B*35:01, HLA-C*03:03, HLA-C*07:02, HLA-C*12:03, HLA-C*14:02) when compared to other peptides.

For **E2** protein 52 peptides were predicted to interact with MHC class I alleles, the peptide **RRRGAAAAL** from 260-268 was found to have high affinity to interact with largest number of alleles (HLA-B*07:02, HLA-B*27:05, HLA-B*39:01, HLA-C*07:02, HLA-C*14:02) followed by the peptide 242 **FVLLVPWVL** 250 which predicted to interact with three alleles (HLA-A*02:01, HLA-A*02:06, HLA-B*39:01).

Analyses of **capsid** protein resulted in 54 peptides interact with different MHC class I alleles. Among these the peptide **FTNLGTPPL** from 174-182 was interacted with highest number of alleles (8 alleles, HLA-A*02:01, HLA-A*02:06, HLA-A*68:02, HLA-B*35:01, HLA-B*39:01, HLA-C*03:03, HLA-C*05:01, HLA-C*14:02). All data are summarized in Table 6.

Prediction of T Helper cell epitopes and interaction with MHC class II

Using MHC class II binding prediction method of IEDB and based on NN align and IC50 of 1000 for E1, E2 and capsid protein. From all predicted epitopes of **E1** protein that bind to MHC class II, the core sequence **FTGVVYGTH** bind to 11 alleles (HLA-DPA1*01:03, HLA-DQA1*05:01, HLA-DRB1*04:01, HLA-DRB1*04:04, HLA-DRB1*04:05, HLA-DRB1*09:01, HLA-DRB1*11:01, HLA-DRB5*01:01, HLA-DPA1*01:03, HLA-DPB1*02:01, HLA-DQB1*03:01) which is largest number of alleles in contrast to other predicted core sequences.

From Analysis of **E2** protein interaction with MHC class II, the

Protein	Peptide	Start	End	Allele	ANN_ic50	Percentile Rank
E1	**YFNPGGSYY**	101	109	HLA-A*29:02	2.71	0.1
				HLA-A*30:02	211.14	0.8
				HLA-B*15:01	149.63	0.7
				HLA-B*15:02	97.86	0.1
				HLA-B*35:01	61.22	0.4
				HLA-B*35:01	61.22	0.4
				HLA-C*03:03	48.33	0.4
				HLA-C*07:02	113.52	0.2
				HLA-C*12:03	23.73	0.2
				HLA-C*14:02	24.06	0.2
	SYFNPGGSY	100	108	HLA-A*29:02	25.81	0.2
				HLA-A*30:02	15.72	0.1
				HLA-B*15:02	43.56	0.1
				HLA-C*07:02	221.79	0.3
				HLA-C*14:02	13.64	0.2
	WAAAHWWQL	442	450	HLA-A*02:06	22.03	0.6
				HLA-A*68:02	58.47	0.7
				HLA-B*08:01	71.79	0.2
				HLA-B*35:01	105.5	0.5
				HLA-B*35:01	105.5	0.5
				HLA-B*39:01	223.35	0.7
				HLA-C*03:03	32.8	0.4
E2	**FVLLVPWVL**	242	250	HLA-A*02:01	56.05	0.5
				HLA-A*02:06	132.05	1.1
				HLA-B*39:01	37.16	0.3
	ALAAFVLLV	238	246	HLA-A*02:01	6.53	0.1
				HLA-A*02:06	26.15	0.6
	RRRGAAAAL	260	268	HLA-B*07:02	245.53	0.5
				HLA-B*27:05	99.39	0.2
				HLA-B*39:01	276.75	0.7
				HLA-C*07:02	165.5	0.3
				HLA-C*14:02	65.77	0.2
CAPSID	**FTNLGTPPL**	174	182	HLA-A*02:01	62.8	0.5
				HLA-A*02:06	20.4	0.6
				HLA-A*68:02	88.4	0.7
				HLA-B*35:01	74.04	0.4
				HLA-B*39:01	69.93	0.3
				HLA-C*03:03	25.95	0.4
				HLA-C*05:01	270.94	0.7
				HLA-C*14:02	31.58	0.2
	ARHPWRIRF	270	278	HLA-B*27:05	31.13	0.2
				HLA-C*06:02	189.85	0.2
				HLA-C*07:01	75.84	0.1
				HLA-C*07:02	74.07	0.2
	IRFGAPQAF	276	284	HLA-B*27:05	124.53	0.3
				HLA-C*06:02	186.4	0.2
				HLA-C*07:01	175.9	0.3
				HLA-C*07:02	120.72	0.2

Table 6: Predicted peptides that interacted with MHC class I alleles from E1, E2 and capsid protein; Remaining data as extra file.

core **FVLLVPWVL** was found to bind to 16 alleles (HLA-DRB1*01:01, HLA-DRB1*04:05, HLA-DRB1*07:01, HLA-DRB1*15:01, HLA-DQA1*05:01, HLA-DRB1*01:01, HLA-DRB5*01:01, HLA-DPA1*01, HLA-DPA1*01:031, HLA-DPA1*01:03, HLA-DPA1*03:01, HLA-DQB1*02:01, HLA-DPB1*02:01, HLA-DPB1*02:0, HLA-DPB1*04:02, HLA-DPB1*04:01), while prediction of **capsid** protein binding to MHC class II revealed that the core **FYRVDLHFT** bound to the highest number of 15 different alleles (HLA-DRB1*01:01, HLA-DRB1*04:01, HLA-DRB1*04:05, HLA-DRB1*07:01, HLA-DRB1*11:01, HLA-DPA1*01, HLA-DPA1*01:03, HLA-DPA1*02:01, HLA-DRB1*01:01, HLA-DPA1*03:01, HLA-DPB1*04:01, HLA-DPB1*04:02, HLA-DPB1*05:01, HLA-DPB1*01:01, HLA-DPB1*02:01). The result is summarized in Table 7.

Protein	Core Sequence	Peptide Sequence	Start	End	Allele	IC50	Percentile Rank
E1	**FTGVVYGTH**	AQSFTGVVYGTHTTA	417	431	HLA-DPA1*01:03/DPB1*02:01	131.3	9.94
					HLA-DQA1*05:01/DQB1*03:01	80.4	12.81
					HLA-DRB1*04:01	343.6	22.48
					HLA-DRB1*04:04	398.4	30.91
					HLA-DRB1*04:05	610.8	32.53
					HLA-DRB1*09:01	258.7	15.83
					HLA-DRB1*11:01	387.6	27.83
					HLA-DRB5*01:01	76.2	13.07
		QSFTGVVYGTHTTAV	418	432	HLA-DPA1*01:03/DPB1*02:01	208.2	13.2
					HLA-DRB1*04:01	304.9	20.66
					HLA-DRB1*04:04	349.2	28.74
					HLA-DRB1*04:05	603.8	32.35
					HLA-DRB1*09:01	211.4	13.54
					HLA-DRB1*11:01	395.1	28.06
					HLA-DRB5*01:01	122.7	17.11
		SFTGVVYGTHTTAVS	419	433	HLA-DRB1*04:04	251.3	23.66
					HLA-DRB1*04:05	801	37.3
					HLA-DRB5*01:01	221.9	23.13
		FTGVVYGTHTTAVSE	420	434	HLA-DRB1*04:04	252.9	23.76
					HLA-DRB1*04:05	792.8	37.11
					HLA-DRB5*01:01	396.1	29.98
	SFTGVVYGT	AQSFTGVVYGTHTTA	417	431	HLA-DPA1*01/DPB1*04:01	96.6	5.16
		QSFTGVVYGTHTTAV	418	432	HLA-DPA1*01/DPB1*04:01	234.9	9.45
		SFTGVVYGTHTTAVS	419	433	HLA-DPA1*01/DPB1*04:01	719.5	18.23
					HLA-DPA1*01:03/DPB1*02:01	642.7	24.47
	TGVVYGTHT	AQSFTGVVYGTHTTA	417	431	HLA-DRB1*01:01	316.8	49.08
		QSFTGVVYGTHTTAV	418	432	HLA-DRB1*01:01	125.5	33.46
		TGVVYGTHTTAVSET	421	435	HLA-DRB1*04:04	368.8	29.6
E2	**FVLLVPWVL**	DHALAAFVLLVPWVL	236	250	HLA-DRB1*01:01	15.4	8.84
					HLA-DRB1*04:05	843.2	38.22
					HLA-DRB1*07:01	597.4	35.94
					HLA-DRB1*15:01	286.5	21.33
					HLA-DQA1*05:01/DQB1*02:01	191.3	4.08
		HALAAFVLLVPWVLI	237	251	HLA-DRB1*01:01	14.4	8.24
					HLA-DRB1*04:05	645.3	33.46
					HLA-DRB1*07:01	489.4	32.97
					HLA-DRB1*15:01	223.6	18.25
					HLA-DQA1*05:01/DQB1*02:01	196.2	4.21
		ALAAFVLLVPWVLIF	238	252	HLA-DRB1*01:01	12.5	7.01
					HLA-DRB1*04:05	638.3	33.28
					HLA-DRB1*07:01	654.9	37.36
					HLA-DRB1*15:01	157.6	14.29
					HLA-DRB5*01:01	895.4	41.52
					HLA-DQA1*05:01/DQB1*02:01	194.3	4.16

		LAAFVLLVPWVLIFM	239	253	HLA-DRB1*01:01	11.1	6.03
					HLA-DRB1*04:05	687.9	34.58
					HLA-DRB1*07:01	849.5	41.58
					HLA-DRB1*15:01	138.9	13.02
					HLA-DRB5*01:01	582.8	35.18
					HLA-DQA1*05:01/DQB1*02:01	223.8	4.9
					HLA-DPA1*01/DPB1*04:01	767.1	18.9
		AAFVLLVPWVLIFMV	240	254	HLA-DRB1*01:01	16.6	9.52
					HLA-DRB1*04:05	726	35.54
					HLA-DRB1*07:01	809	40.76
					HLA-DRB1*15:01	134.6	12.7
					HLA-DRB5*01:01	722.7	38.28
					HLA-DQA1*05:01/DQB1*02:01	370.4	8.38
					HLA-DPA1*01/DPB1*04:01	727.9	18.35
		AFVLLVPWVLIFMVC	241	255	HLA-DRB1*01:01	25.1	13.58
					HLA-DRB1*04:05	823.8	37.78
					HLA-DRB1*15:01	172.9	15.3
					HLA-DQA1*05:01/DQB1*02:01	493.7	11.04
		FVLLVPWVLIFMVCR	242	256	HLA-DRB1*01:01	39.2	18.41
					HLA-DRB1*15:01	196.8	16.77
					HLA-DQA1*05:01/DQB1*02:01	720.8	15.57
	RWGLPPWEL	RFGCAMRWGLPPWEL	169	183	HLA-DRB1*07:01	909.5	42.7
		FGCAMRWGLPPWELV	170	184	HLA-DRB1*01:01	478.6	56.04
					HLA-DRB1*07:01	711.9	38.7
					HLA-DPA1*01:03/DPB1*02:01	320.1	16.88
		GCAMRWGLPPWELVV	171	185	HLA-DRB1*01:01	264.9	45.91
					HLA-DRB1*07:01	870.6	41.96
					HLA-DPA1*01:03/DPB1*02:01	251.3	14.72
		CAMRWGLPPWELVVL	172	186	HLA-DRB1*01:01	101.3	30.36
					HLA-DRB1*07:01	837.2	41.34
					HLA-DPA1*01:03/DPB1*02:01	199.1	12.85
					HLA-DPA1*03:01/DPB1*04:02	875.2	30.17
		AMRWGLPPWELVVLT	173	187	HLA-DRB1*01:01	126.8	33.61
					HLA-DPA1*01:03/DPB1*02:01	232.7	14.07
		MRWGLPPWELVVLTA	174	188	HLA-DRB1*01:01	196.3	40.57
					HLA-DPA1*01:03/DPB1*02:01	342.5	17.52
		RWGLPPWELVVLTAR	175	189	HLA-DPA1*01:03/DPB1*02:01	539.2	22.36
	LWLATANAL	CSPASALWLATANAL	219	233	HLA-DRB1*01:01	14.2	8.11
					HLA-DRB1*04:01	247.4	17.67
					HLA-DRB1*04:05	450.7	27.65
					HLA-DRB1*07:01	25	4.83
					HLA-DRB1*13:02	155.6	8.31
					HLA-DRB1*15:01	497.2	28.97
					HLA-DRB5*01:01	266.6	25.22
					HLA-DQA1*04:01/DQB1*04:02	623.5	9.9
					HLA-DQA1*05:01/DQB1*03:01	54.4	9.59
					HLA-DPA1*01:03/DPB1*02:01	866.2	28.4
					HLA-DPA1*02:01/DPB1*01:01	601.2	33.75
					HLA-DPA1*03:01/DPB1*04:02	887.8	30.35

CAPSID	**FYRVDLHFT**	EGEGAVFYRVDLHFT	161	175	HLA-DRB1*01:01	42.9	19.44
					HLA-DRB1*04:01	291.4	20
					HLA-DRB1*04:05	106.5	10.16
					HLA-DRB1*07:01	581.1	35.52
					HLA-DRB1*11:01	492.3	30.86
					HLA-DPA1*01/DPB1*04:01	674.9	17.6
					HLA-DPA1*01:03/DPB1*02:01	329.5	17.15
					HLA-DPA1*02:01/DPB1*01:01	180.1	16.49
					HLA-DPA1*02:01/DPB1*05:01	768	14.63
		GEGAVFYRVDLHFTN	162	176	HLA-DRB1*01:01	31.6	16.02
					HLA-DRB1*04:05	75.1	7.39
					HLA-DRB1*07:01	743.7	39.39
					HLA-DPA1*01/DPB1*04:01	577.7	16.16
					HLA-DPA1*01:03/DPB1*02:01	321.1	16.91
					HLA-DPA1*02:01/DPB1*01:01	149.1	14.33
					HLA-DPA1*02:01/DPB1*05:01	408.4	8.72
		EGAVFYRVDLHFTNL	163	177	HLA-DRB1*01:01	19.7	11.15
					HLA-DRB1*04:05	61.9	6.1
					HLA-DRB1*07:01	626	36.64
					HLA-DPA1*01/DPB1*04:01	330.1	11.65
					HLA-DPA1*01:03/DPB1*02:01	201.1	12.92
					HLA-DPA1*02:01/DPB1*01:01	104.3	10.77
					HLA-DPA1*02:01/DPB1*05:01	245.3	5.44
		GAVFYRVDLHFTNLG	164	178	HLA-DRB1*01:01	16.1	9.25
					HLA-DRB1*04:05	70.6	6.96
					HLA-DPA1*01/DPB1*04:01	212.1	8.87
					HLA-DPA1*01:03/DPB1*02:01	194	12.65
					HLA-DPA1*02:01/DPB1*05:01	217.7	4.81
		AVFYRVDLHFTNLGT	165	179	HLA-DRB1*01:01	25	13.55
					HLA-DRB1*04:05	73.5	7.23
					HLA-DPA1*01/DPB1*04:01	248.7	9.78
					HLA-DPA1*01:03/DPB1*02:01	192.8	12.6
					HLA-DPA1*02:01/DPB1*05:01	174	3.81
		VFYRVDLHFTNLGTP	166	180	HLA-DRB1*01:01	43.4	19.57
					HLA-DRB1*04:05	105.8	10.11
					HLA-DPA1*01/DPB1*04:01	286.8	10.69
					HLA-DPA1*01:03/DPB1*02:01	244.7	14.49
					HLA-DPA1*02:01/DPB1*05:01	190.1	4.19
		FYRVDLHFTNLGTPP	167	181	HLA-DRB1*01:01	79.7	27.11
					HLA-DRB1*04:05	146.9	13.18
					HLA-DPA1*01/DPB1*04:01	462.2	14.23
					HLA-DPA1*01:03/DPB1*02:01	506.6	21.64
					HLA-DPA1*02:01/DPB1*01:01	366.2	25.91
					HLA-DPA1*02:01/DPB1*05:01	406.6	8.68
					HLA-DPA1*03:01/DPB1*04:02	313.3	18.79

	FGAPQAFLA	HPWRIRFGAPQAFLA	272	286	HLA-DRB1*04:01	232.4	16.86
					HLA-DRB1*04:04	336.3	28.13
					HLA-DRB5*01:01	290.5	26.22
		PWRIRFGAPQAFLAG	273	287	HLA-DRB1*04:01	218.2	16.06
					HLA-DRB1*04:04	300.3	26.3
					HLA-DRB5*01:01	333.4	27.85
					HLA-DQA1*01:02/DQB1*06:02	434.4	24.97
		WRIRFGAPQAFLAGL	274	288	HLA-DRB1*04:01	202.8	15.17
					HLA-DRB1*04:04	309.7	26.79
					HLA-DRB1*09:01	36.3	2.08
					HLA-DRB5*01:01	248.9	24.44
					HLA-DQA1*01:02/DQB1*06:02	316.2	20.06
		RIRFGAPQAFLAGLL	275	289	HLA-DRB1*01:01	22.2	12.33
					HLA-DRB1*04:01	210.1	15.6
					HLA-DRB1*09:01	38.7	2.29
					HLA-DRB1*11:01	811.4	37.68
					HLA-DRB5*01:01	273.1	25.5
					HLA-DQA1*01:02/DQB1*06:02	345.9	21.39
					HLA-DPA1*02:01/DPB1*01:01	302.4	23.17
		IRFGAPQAFLAGLLL	276	290	HLA-DRB1*01:01	42.2	19.25
					HLA-DRB1*04:01	409.4	25.31
					HLA-DRB1*09:01	65.4	4.42
					HLA-DRB5*01:01	675.9	37.28
					HLA-DQA1*01:02/DQB1*06:02	410.8	24.05
					HLA-DPA1*01:03/DPB1*02:01	234.8	14.15
		RFGAPQAFLAGLLLA	277	291	HLA-DRB1*01:01	57.7	23
					HLA-DRB1*04:01	676.2	34.57
					HLA-DRB1*09:01	104.2	7.18
					HLA-DQA1*05:01/DQB1*03:01	44.9	8.22
	EGAVFYRVD	WLWSEGEGAVFYRVD	157	171	HLA-DQA1*03:01/DQB1*03:02	252	3.75
		LWSEGEGAVFYRVDL	158	172	HLA-DQA1*03:01/DQB1*03:02	252.1	3.76
		WSEGEGAVFYRVDLH	159	173	HLA-DQA1*03:01/DQB1*03:02	295.6	4.63
		SEGEGAVFYRVDLHF	160	174	HLA-DRB1*01:01	758.6	63.18
					HLA-DQA1*03:01/DQB1*03:02	346.6	5.65
		EGEGAVFYRVDLHFT	161	175	HLA-DQA1*03:01/DQB1*03:02	491.9	8.54
		GEGAVFYRVDLHFTN	162	176	HLA-DQA1*03:01/DQB1*03:02	840.3	14.99

Table 7: Result of predicted peptides from structural proteins that interact with MHC class II alleles; Remaining data as extra file.

Analysis of population coverage

All epitopes from the three structural proteins which selected as epitopes with high affinity to interact with MHC class I and MHC class II, subjected to IEDB population coverage set against the whole world population.

For MHC class I, Epitopes with highest population coverage were **YFNPGGSWW** (54.08%), **FVLLVPWVL** (42.23%) and **FTNLGTPPL** (58.29%) for E1, E2 and capsid protein respectively. Data displayed in Table 8.

In MHC class II, the epitopes that interact with class II alleles and showed highest population coverage were found to be **FTGVVYGTH** (93.05%), **FVLLVPWVL** (99.95%) and **FYRVDLHFT** (99.93%) for E1, E2 and capsid respectively, as shown in Table 9. The epitope **FVLLVPWVL** form E2 protein is interacted with both MHC I and MHC II with high affinity and highest population coverage for each class. All these proposed peptides are illustrated in Figure 3 at structural level.

The combined coverage of MHC I and MHC class II

Using IEDB and population coverage prediction tools, the top three peptides that interact with most frequent alleles for both MHC class I and class II for each protein were analyzed and the result showed

epitope set of **98.54%** and **99.99%** for **E1** and **E2** respectively, while combined population coverage of epitopes from **capsid protein** displayed an epitope set of **100%.** The data demonstrated in Table 10.

Prediction of population coverage was also calculated for combined MHC class I and class II using proposed epitopes from **ALL** three protein (E1, E2 and capsid protein) which resulted in epitope set of 100%. The data was displayed in Table 11.

Discussion

The aim of this study is to identify potential epitopes that can induce cellular and humoral immune reaction and act as candidate for rubella vaccine development. We used Immuno informatics tools to identify epitopes for multiple peptide vaccine, these tools was recently used to design vaccines for many viruses such as Ebola [42], Zika virus [43], merkel cell polyomavirus [44] and human papillomavirus [45]. Rubella virus contains two projections that are mainly protein in nature, E1 and E2, which anchored to the outer layer of the membrane and many forms of nucleocapsid envelope protein. The E1 protein is the immunodominant antigen and also plays role in endocytosis and viral neutralization [46-48]. Babies with congenital rubella syndrome showed proliferative response against E2, and significant proportion showed proliferative response against capsid protein, while antibodies response was mainly directed against E1 followed by E2 and capsid protein [49,50]. Immunoglobulin has been used in attempts to prevent rubella in pregnant women exposed to the virus. However, it does not appear to be highly effective [46]. The first step in the infection is the membrane fusion of E1 an E2 with the enhancement of capsid protein [51]. Fusion of the viral envelope occurs when conformational change of E1 and E2 proteins induced by exposure to pH of 6 or less [52]. Our proposed peptides form three proteins are 100% conserved regions in proteins as well as succeeded all subjected tests for B cell and also bound to MHC alleles with high affinity.

Protein	epitope	Coverage class I	Total HLA hits
E1	**YFNPGGSYY**	54.08%	9
	SYFNPGGSY	30.66%	5
	WAAAHWWQL	30.61%	6
E2	**FVLLVPWVL**	42.23%	3
	ALAAFVLLV	40.60%	2
	RRRGAAAAL	39.13%	5
Capsid	**FTNLGTPPL**	58.29%	8
	ARHPWRIRF	52.96%	4
	IRFGAPQAF	52.96%	4

Table 8: Population coverage of proposed peptide interacted with MHC class I from the three proteins; Remaining data as extra file.

Protein	epitope	Coverage class II	Total HLA hits
E1	**FTGVVYGTH**	93.05%	10
	SFTGVVYGT	84.37%	4
	TGVVYGTHT	16.02%	2
E2	**FVLLVPWVL**	99.95%	25
	RWGLPPWEL	99.77%	21
	LWLATANAL	99.59%	22
capsid	**FYRVDLHFT**	99.95%	28
	FGAPQAFLA	99.87%	26
	EGAVFYRVD	99.75%	17

Table 9: MHC class II Population coverage of proposed peptides; Remaining data as extra file.

Protein	epitope	Coverage class I and II	Total HLA hits	Epitope set
E1	YFNPGGSYY	54.08%	9	**98.54%**
	SYFNPGGSY	30.66%	5	
	WAAAHWWQL	30.61%	6	
	FTGVVYGTH	93.05%	10	
	SFTGVVYGT	84.37%	4	
	TGVVYGTHT	11.53%	3	
E2	ALAAFVLLV	40.60%	2	**99.99%**
	RRRGAAAAL	39.13%	5	
	FVLLVPWVL	99.97%	28	
	RWGLPPWEL	99.77%	21	
	LWLATANAL	99.10%	17	
capsid	FTNLGTPPL	58.29%	8	**100%**
	ARHPWRIRF	52.96%	4	
	IRFGAPQAF	52.96%	4	
	FYRVDLHFT	99.95%	28	
	EGAVFYRVD	99.75%	17	
	FGAPQAFLA	99.75%	24	

Table 10: Combined population coverage of MHC class I and class II for proposed peptides from each protein.

epitope	Coverage class I and II	Total HLA hits
YFNPGGSYY	54.08%	9
SYFNPGGSY	30.66%	5
WAAAHWWQL	30.61%	6
FTGVVYGTH	93.05%	10
SFTGVVYGT	84.37%	4
TGVVYGTHT	11.53%	3
ALAAFVLLV	40.60%	2
RRRGAAAAL	39.13%	5
FVLLVPWVL	99.97%	28
RWGLPPWEL	99.77%	21
LWLATANAL	99.10%	17
FTNLGTPPL	58.29%	8
ARHPWRIRF	52.96%	4
IRFGAPQAF	52.96%	4
FYRVDLHFT	99.95%	28
EGAVFYRVD	99.75%	17
FGAPQAFLA	99.75%	24
Epitope set	**100.00%**	

Table 11: Combined population coverage of MHC class I and class II for proposed peptides from all three proteins E1, E2 and capsid protein.

Rubella **E1** protein was subjected to IEDB B cell epitope prediction tests. It was found that the most satisfactory peptide is 8 amino acid **PVCQRHSP** B cell epitope from 233 to 240 with antigenicity score of 1.116 and 1.167 Score for Emini surface accessibility. Mitchell et al. measured specific IgG antibodies level before and after reimmunization with MMR vaccine and found similar result as E1(234-252) peptide contain antibody neutralizing domain [12], while E1(208-239) bind effectively to monoclonal antibodies in study done by Wolinsky et al. using mice and rabbit immunized by this peptide [53]. While 12 Epitopes from **E1** Protein interacted with MHC class I HLA alleles. The proposed T cell peptide **101 YFNPGGSSY 109** is well conserved among Rubella E1 protein. It was identified using IEDB MHC I prediction tool. Yang et al. found that the peptide between the 81 and 109 in E1 protein involved in the membrane fusion activity of the virus [54] reflected the importance of this protein for the virus. Chong et al. reported that T cell epitopes are mainly located in E1 and capsid protein

but less in E2, but they recognized different peptides from E1, E1(207-226), E1(324-343) and E1(358-377) that can stimulate cellular immune response [55], our peptide predicted to bind to 10 different HLA alleles (HLA-A*29:02, HLA-A*30:02, HLA-B*15:01, HLA-B*15:02, HLA-B*35:01, HLA-B*35:01, HLA-C*03:03, HLA-C*07:02, HLA-C*12:03, HLA-C*14:02) with high affinity by MHC prediction tool. Ovsyannikova et al. analyzed HLA class I type in group of children who received second dose of MMR and they reported other alleles, their result showed that HLA-B 3503 and HLA-CW 1502 were associated with T cell response against the vaccine [56]. All epitopes were tested using population coverage tool of IEDB which measure the percentage of people in whole world who have potential to develop immune response to vaccine contains this epitope. Our proposed peptide that binds to MHC 1 alleles had coverage of **54.08%** which is the highest figure among all predicted peptides. On another handout of seven Predicted peptides our proposed core **FTGVVYGTH** is part of different peptide sequence in **E1** protein from 417 to 434, interact with 11 MHC class II HLA alleles with high affinity, Mitchell et al. found increase in simulation indices after MMR vaccine for different E1 peptides, E1(213-239), (234-252), (254-285), (272-285), (301-314) and (462-481) [12]. Ovsyannikova et al. tested the association between HLA class II and cellular and humoral immune response after rubella vaccine in 346 children and found that DPB1*0301, DQB1*0501, DRB1*0101, and DRB1*1104 associated with cellular immune response [57], which are different from what we predicted using this epitope. Our core sequence has potential population coverage of **93.05%** which considered as promising coverage for vaccine that will contain this epitope. Rubella peptides induce protective neutralizing antibodies [46], that considered to be protective in contrast to measles vaccine which does not prevent infection or disease [58].

Among all predicted **E2** epitopes from only conserved region as in Table 5 which subjected to Bepipred linear epitope prediction, Emini surface accessibility and Kolaskar and Tongaonker antigenicity, the epitope **AQYPP** from 163 to 167 Had highest score in both test of 2.363 in surface accessibility and 1.074 in antigenicity test, and chosen as proposed peptide from E2 protein that can activate B cell to produce antibodies against the virus. In contrast, Mitchell et al. reported that E2 (1-16) and E2 (10-36) had domain that can neutralize antibodies [12]. T cell immune response is essential for longer lasting response [59]. For **E2** protein, among all 52 conserved predicted epitopes which interact with high affinity to MHC class I as summarized in Table 6, the epitope **FVLLVPWVL** from 242 to250 was found to had high affinity to interact with three MHC class I alleles, which is dissimilar to E2(1-16), (10-36), (35-58), (50-72), (134-150), (140-156), (168-179) and (248-260) that stated to have cellular immune response as reported by Mitchell et al. [12]. Our proposed peptide has highest world population coverage of 42.23%. **The same epitope** had also the highest affinity to interact to different 16 MHC class II alleles (HLA-DRB1*01:01, HLA-DRB1*04:05, HLA-DRB1*07:01, HLA-DRB1*15:01, HLA-DQA1*05:01, HLA-DRB1*01:01, HLA-DRB5*01:01, HLA-DPA1*01, HLA-DPA1*01:031, HLA-DPA1*01:03, HLA-DPA1*03:01, HLA-DQB1*02:01, HLA-DPB1*02:01, HLA-DPB1*02:0, HLA-DPB1*04:02, HLA-DPB1*04:01), out of 59 predicted core sequences. Ovsyannikova et al. found association between HLA class II alleles and T cell response specifically DRB1 (DRB1*0101, DRB1*0701, and DRB1*1104), DQB1(DQB1*0202 and DQB1*0501) and DPB1 (DPB1*0301,DPB1*0401, DPB1*1001 and DPB1*1101) response to MMR vaccine [57] which have some alleles in common with our study. This core resulted in population coverage of 99.59% as predicted by IEDB and 99.97% for combined MHC I and MHC II worldwide coverage. The greatest results for both classes make it promising epitope for vaccine design as it able to induce T cell immune response.

The **capsid protein** is part of host interaction and important for virus assembly [51]. It undergoes a structural change permitting release of viral genomic RNA into the cytoplasm [52]. Nine epitopes from only conserved region was found to interact with B cell, epitope**258PPHT261** represented the proposed epitope with high Emini surface accessibility and antigenicity score of 1.285 and 1.036 respectively. Few studies conducted about capsid protein as protein for vaccine design, but Lovett et al. reported that capsid peptide C (1-29) contain T cell epitope that help in antibodies production [60]. In comparing to all 54 epitope from conserved regions which interacted with MHC I alleles, epitope 174 **FTNCGTPPL** 182 bind to 8 alleles (HLA-A*02:01, HLA-A*02:06, HLA-A*68:02, HLA-B*35:01, HLA-B*39:01, HLA-C*03:03, HLA-C*05:01, HLA-C*14:02). Chong et al. recognized T cell epitopes in capsid (119-152), (205-233) and (255-280) [55] which similar to some predicted peptides but different from our proposed peptide. With potential population coverage of **58.29%**, this peptide considered as candidate for vaccine production. The core **FYRVDLHFT** has high score among 51 conserved epitopes that interacted with MHC II alleles by binding to 15 Alleles. In contrast to Capsid peptide (11-29) that was promiscuously recognize HLA class II restricted CD4 T cell as reported by Lovett et al. [60] our peptide resulted in very high population coverage of 99.95%. To get maximum benefits of vaccine we predicted the population coverage of combined T cell epitopes in Tables 6 and 7 for each protein and the results were promising, with epitope set of 98.54% for E1, 99.99% for E2, and 100% for capsid protein. Furthermore vaccine that contains the top three epitopes from all structural protein predicted to have 100% coverage in the whole world reflecting the favorable effect of this vaccine.

The efficacy and safety of predicted epitopes by this computational analysis are needed to be evaluated by animal model studies, to confirm whether they can induce protective immune response or not. There are only six sequences of E2 and capsid proteins available in the database; more sequences are needed to increase the significance of the result. The following proposed peptides are recommended for multiple peptides vaccine design against rubella virus; (PVCQRHSP from 233 to 240, YFNPGGSYY from 101 to 109 and the core FTGVVYGTH) from E1. (AQYPP from 163 to 167 and FVLLVPWVL from 242 to 250) from E2, (PPHT from 258 to 261, FTNLGTPPL from 174 to 182, and the core FYRVDLHFT) from capsid protein. This vaccine will insure good population coverage and fewer side effects that can be seen with life attenuated vaccine.

Conclusion

The efficacy and safety of predicted epitopes by this computational analysis are needed to evaluate animal model studies, to confirm whether they can induce protective immune response or not. There are only six sequences of E2 and capsid proteins available in the database; more sequences are needed to increase the significance of the result. The following proposed peptides are recommended for multiple peptides vaccine design against rubella virus; (PVCQRHSP from 233 to 240, YFNPGGSYY from 101 to 109 and the core FTGVVYGTH) from E1. (AQYPP from 163 to 167 and FVLLVPWVL from 242 to 250) from E2, (PPHT from 258 to 261, FTNLGTPPL from 174 to 182, and the core FYRVDLHFT) from capsid protein. This vaccine will insure good population. Coverage and fewer side effects that can be seen with life attenuated vaccine.

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