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Species, population and age diversity in cell resistance to adhesion of *Neisseria meningitidis* serogroups A, B and C

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ABSTRACT – The variation of cell adherence of meningococci serogroups A, B and C and influenza viruses was investigated in 11 animal species and in humans of different age groups (1st, 2nd, 3rd and 4th weeks; 2nd-3rd months; 4th-12th months, 2nd-3rd years; and 18th-60th years of life) as well as in women during pregnancy (17th-36th weeks) and childbirth. Red blood cells of all animals tested as well as of human newborns were absolutely resistant to attachment of meningococci. In neonatal and the later periods the human cells become far differently sensitive individually to meningococcal adhesion. In contrast, the viral adhesion was characterized by different individual cell sensitivity in all age groups tested. Pregnancy and childbirth did not influence the women's cell sensitivity to adhesion of *Neisseria meningitidis*. Different receptors are involved in interactions of human cells with influenza viruses and meningococci. The function of meningococcal receptors on human cells develops during postnatal ontogenesis. The variations express both specific (genetic) and ontogenetic (individual) differences in natural resistance to meningococcal infection. © 2000 Éditions scientifiques et médicales Elsevier SAS

adhesion / biodiversity / natural immunity / individuality / influenza / *Neisseria meningitidis* / newborn's infections / receptors

1. Introduction

Despite considerable molecular, immunological and epidemiological efforts and increased understanding of how meningococcal infection develops, the disease remains a potentially life-threatening emergency capable of causing significant morbidity and mortality. Many key questions concerning the epidemiological and clinical patterns of meningococcal infection remain unanswered. Some of the questions are the species specificity, age and individual differences of humans in natural susceptibility to *Neisseria meningitidis* infection. Meningococci are carried as harmless commensals in the nasopharynx in about 1% of the population. In some individuals, namely in only a small proportion of carriers, however, the same microbe causes devastating and fatal illness [1]. The reasons of this selectivity are unknown.

One of the most interesting questions is the resistance all of animals and children under one month to the disease [2, 3] in contrast, for instance, to influenza infections that are not uncommon at the same age [4].

A general characteristic of most infections is the changed resistance to disease that develops in the course of growth and maturation of the possible victim. The changes are particularly dramatic in the neonatal period. Most infections, for instance influenza, can be very severe in the neonatal period. Meningococcal infection presents one of the rare exceptions to this common law. About 15 per cent of all cases of childhood meningitis are due to the meningococcus [3], children under one month very seldom are known to fall ill with meningococcal infection. In a large series of 211 cases of neonatal meningitis, *N. meningitidis* was an uncommon organism. Only two of 211 were due to *N. meningitidis* [2]. The nature, determinants, origin and genesis of the above phenomenon of newborn resistance to meningococcal infection and what factors are it conditioned by are unknown.

Several explanations of age-dependent change in age variation of inborn immunity have been advanced: maturation of the lymphatic immunogenic system; develop-

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ment of 'barriers' to the spread of microbe from the periphery to highly susceptible target organs; augmentation in interferon productivity; maturation of macrophages; higher and more stable body temperature [2, 3]; inherent variation in the complement pathway [5]. The extreme rarity of meningococcal infection in the newborn period is not inconsistent with transplacental immunity [3].

On the other hand, there are assumptions that the nature of discussed phenomenon is associated with some peculiarities of the age of the organism's molecular constitution, that do not involve the reactive production of immunoglobulins [6–9], e.g., inherent differences in cellular receptor structures should be responsible for the agent's adhesion which in most cases is the key stage of infectious processes [10]. Age-related changes in resistance of cells to mengovirus and encephalomyocarditis virus are conditioned by corresponding changes in maturation of the cell membrane molecular composition, namely the structure of molecular receptor [7]. Erythrocytes of two-day-old chickens are more sensitive to rabies virus adhesion than those of adult chickens [11]. Malaria parasites demonstrate selectivity towards a particular age group of erythrocytes. Young mature chicken erythrocytes are selectively attacked by *Plasmodium gallinaceum*. Erythrocytes under 12 days of age are being preferentially destroyed by the parasites [6]. A factor involved in such a phenomenon may be that the young erythrocytes contain more lipids in their membrane than the old cells. There might be factors that prevent the plasmodium from entering cells of a certain age due to change in the red cell surface receptor sites that are known to bind merozoites [6]. Age-determined distinctions of cell sensitivity to meningococci have not been investigated. So, the reason for low morbidity in children under one month is still unclear.

Infections due to intracellular parasites, *N. meningitidis* included, involve at least three sequential steps: 1) adhesion of microbe to plasma cell membrane; 2) translocation of the microbe into cell plasma; 3) reproduction of the microbe in the cytoplasma of the cell. Only microbes capable of adhering to the cell's outer membrane are capable of penetrating the membrane and introducing themselves into cytoplasma of the cell [10]. Adhesion of most pathogenic microbes, *N. meningitidis* included, on the victim cell's surface is a starting, i.e., key step in development of the infectious process. A crucial property of the pathogenicity of meningococcal infection is the ability to adhere to human target cells [12]. The potential of *N. meningitidis* to cause systemic disease is dependent on its ability to attach to relevant tissues and cells. Most *N. meningitidis* strains express pili responsible for interaction with and adherence to epithelial and mesenchymal cells, especially to endothelial and blood cells [12, 13, 14]. The characteristics of adherence which allow meningococcus to reside on cell surfaces are of interest because these microbes have been associated with very heavy disease states.

The present investigation focuses on some conditions that are involved in adhesion of N. meningitidis and influenza viruses to red blood cells of humans and animals. The rationale of the comparison of meningococci with influenza viruses was determined by sharp differences in their incidence in the prenatal and newborn period of ontogenesis. Erythrocytes were chosen because they represent a most convenient experimental model for studying microbial adhesion [15]; besides, there are well-known difficulties in obtaining infant cells of other types. Previous investigations revealed the correlation between adhesive potencies of erythrocytes, leukocytes and epitheliocytes as well as of other target cells [13–16].

The chief aim of the present work was adherence of meningococci and influenza viruses to the cells of adult animals and the cells obtained from humans of different age groups and women during pregnancy and childbirth. The rationale of the comparison of human and animals was determined by differences in their susceptibility to natural meningococcal infection.

2. Materials and methods

The adhesion of meningococci to cells investigated in a selection of 11 animal species (mice, guinea pigs, rats, Syrian hamsters, rabbits, goats, sheep, donkeys, horses, bulls, hens) and in different human age groups (1st, 2nd, 3rd and 4th weeks; 2nd-3rd months; 4th-12th months, 2nd-3rd years; and 18th-60th years of life) as well as in women during pregnancy (17th-36th weeks) and childbirth. The examination was carried out in healthy individuals. Human red blood cells for each sample were obtained from the blood of the umbilical vein (newborn children) or from the finger of older individuals under study. Animal blood cells were obtained from relevant veins.

Meningococcal and influenza virus adhesion was estimated on the basis of erythrocyte haemagglutination (HA-test) according to Goldhar [15]. A quantitative microassay of cell susceptibility to adhesion of *N. meningitidis* serogroups A, B and C was performed using the preparations of meningococcal adhesins produced by the Institute of Vaccines and Sera (Saint-Petersburg, Russia). The preparations are lyophilised suspensions of killed meningococci of the above serogroups prepared from selected cultures of high adhesive activity tested with human epitheliocytes, leukocytes and erythrocytes. To estimate the adhesion of influenza viruses, lyophilised suspensions of killed virions were used. They were prepared by the Institute of Vaccines and Sera (Saint-Petersburg, Russia) using A/Leningrad/289/83H3N3 and B/Leningrad/90/86 strains. All of the adhesin preparations used were stabilised by lyophilization to provide good test standardization.

All the preparations were standardised as to their adhesive activity, which was expressed in haemagglutination units (HAU). Freshly rehydrated microbial preparations of standardised adhesive capability, twofold diluted, were mixed with erythrocyte suspensions (3.6%) in phosphate-buffered saline (pH 7.2). In this way, the test was arranged to avoid the antiadhesive influence of any humoral factors. Index of adhesion was determined as a reciprocal of minimal quantity of adhesin preparation (HAU) at which haemagglutination occurred. The individual samples of blood plasma were examined for antiadhesive substances, testing the influence of meningococcal adhesins on agglu-

Table I. Resistance to adhesion of *N.meningitidis* A, B, and C in a selection of *Vertebrata* species.

Animal species	*Number of individuals tested*	*Meningococci*	*Indices of adhesion and their incidence (%)*							
			0.06	*0.12*	*0.25*	*0.5*	*1.0*	*2.0*	*4.0*	*8.0*
Mice	8	A	0	0	0	0	0	0	0	0
	8	B	0	0	0	0	0	0	0	0
	5	C	0	0	0	0	0	0	0	0
Guinea pigs	8	A	0	0	0	0	0	0	0	0
	8	B	0	0	0	0	0	0	0	0
	5	C	0	0	0	0	0	0	0	0
Rats	5	A	0	0	0	0	0	0	0	0
	5	B	0	0	0	0	0	0	0	0
	5	C	0	0	0	0	0	0	0	0
Syrian hamster	1	A	0	0	0	0	0	0	0	0
	1	B	0	0	0	0	0	0	0	0
Rabbits	24	A	0	0	0	0	0	0	0	0
	24	B	0	0	0	0	0	0	0	0
	5	C	0	0	0	0	0	0	0	0
Goats	17	A	0	0	0	0	0	0	0	0
	17	B	0	0	0	0	0	0	0	0
	5	C	0	0	0	0	0	0	0	0
Sheep	17	A	0	0	0	0	0	0	0	0
	17	B	0	0	0	0	0	0	0	0
	5	C	0	0	0	0	0	0	0	0
Donkeys	17	A	0	0	0	0	0	0	0	0
	17	B	0	0	0	0	0	0	0	0
	5	C	0	0	0	0	0	0	0	0
Horses	6	A	0	0	0	0	0	0	0	0
	6	B	0	0	0	0	0	0	0	0
	3	C	0	0	0	0	0	0	0	0
Bull	1	A	0	0	0	0	0	0	0	0
	1	B	0	0	0	0	0	0	0	0
	1	C	0	0	0	0	0	0	0	0
Hens	14	A	0	0	0	0	0	0	0	0
	14	B	0	0	0	0	0	0	0	0
	4	C	0	0	0	0	0	0	0	0

tination of susceptible erythrocytes. Antiadhesive activity of plasma was examined by mixing it with adhesin preparations (1 HAU) succeeded by tests with standard lyophilised erythrocytes of high sensitivity to adhesion.

3. Results

Susceptibility of animal cells to meningococcal adhesion was examined in 8 mice, 8 guinea pigs, 5 rats, 1 Syrian hamster, 24 rabbits, 17 goats, 17 sheep, 17 donkeys, 5 horses, 3 cows, 14 hens, 1 bull *(table I)*. There is no *N. meningitidis* adhesive interaction with erythrocytes of any of the animals tested. All the applied concentrations of meningococcal adhesins of the three serogroups failed to agglutinate the erythrocytes of all of the animals used. All samples of animal erythrocytes were extremely resistant to adhesion of *N. meningitidis* serogroups A, B and C (index of adhesion < 0.06).

In humans, the cell susceptibility to meningococcal adhesion was examined in 103 newborn children until seven days of age; 20 children at the age of 2–4 weeks; 19 children of 2–3 months; 23 children of 4–12 months; 44 children of 2–3 years; 5 286 adults of 18–60 years; 11 women during pregnancy (17–36 weeks) and 11 women during childbirth.

Erythrocytes of the adults, including pregnant women and those in childbirth, displayed individually variable agglutinability by meningococcal adhesins *(tables II* and *III)*. The individual ability of cells of 137 surveyed adults to adhere to meningococci was characterized by indices of adhesion from 0.12 up to 2 – a more than 16-fold difference *(table II)*. In a large group (5149 young men) tested for adhesion of *N. meningitidis* B the indices of adhesion varied from 0.12 up to 16 – a more than 128-fold difference. Meanwhile the adhesin treatment of some human erythrocytes resulted in agglutination only when the adhesin concentration was more than 128 times that used for erythrocytes of other individuals *(table II)*. Among the pregnant women and women during childbirth various degrees of sensitivity also came to light *(table III)*.

The revealed range of individual distinctions demonstrated impressive heterogeneity of adults in sensitivity to adhesion of meningococci. Some adults displayed sensitivity to all three adhesins tested (A, B and C), whereas others were sensitive to one or two of them. The analogous

Table II. Variability of adults' erythrocyte sensitivity to adhesion of *N. meningitidis* groups A, B and C.

Meningococci	*Number of individuals tested*	*Indices of adhesion and their incidence (%)*								*Range of individual distinctions*
		0.06	*0.12*	*0.25*	*0.5*	*1.0*	*2.0*	*4.0*	*8.0*	*16.0*	
A	137	0	2	8	64	21	5	0	0	0	16
B	137	0	20	30	39	10	1	0	0	0	16
C	137	0	9	18	53	19	2	0	0	0	16
B	5149	0	2	5	13	32	30	12	3	2	128

variations of individual susceptibility to adhesion was observed by testing of human leukocytes and epitheliocytes *[16]* Individual ability of adults to adhesion of meningococci was stable over a period of five years. Cells of the four human blood types (A, B, O) failed to reveal significant differences. Examination of the blood plasma did not reveal any humoral antiadhesive capacity.

The agglutination of the newborn children's cells was in contrast with those of adults *(table IV)*. Compared with cells of older individuals, the erythrocytes of newborn children were extremely resistant to adhesion of *N. meningitidis* serogroups A, B and C (index of adhesion < 0.06). All the concentrations of meningococcal adhesins failed to agglutinate the erythrocytes of all newborns tested. None of 103 newborn children had an index of adhesion equal to or more than 0.06. Plasma from newborn children as well as from pregnant women and other adult persons did not reveal any antiadhesive humoral factors. Adhesion of *N. meningitidis* to human red blood cells appears to be age dependent.

The results of agglutination of the newborn children's cells by influenza viruses were not in agreement with the above observations. The individual cell susceptibility to adhesion of influenza viruses type A and B was examined in 20 newborn children and 29 adults of 20–60 years of age *(table V)*. Erythrocytes of newborn children and adults were sensitive to adheson of influenza A and B viruses but to different extent. Erythrocytes of children had individually variable sensitivity to agglutination by influenza viruses at the moment of birth. The indices of adhesive ability of the adults and children did not in essence differ from each other. In the two age groups tested, both high and low individual sensitivity to viral adhesion was revealed. Thus, the adhesion of influenza viruses to human red blood cells is age independent.

The minimal susceptibility of some children to adhesion of meningococci and its individual variability was noted only after the first week of life. After the first week, the children's erythrocytes responded to maximum concentration of adhesin A in only 1 of 6 cases. The range of population diversity was minimal (*table IV*; range of individual distinctions: 2). Meanwhile all the concentrations of meningococcal adhesins of serogroups B and C failed to agglutinate the erythrocytes of all children tested during the second week of their life; individual differences were not revealed (*table IV*; index of adhesion: < 0.06).

During the third week of life erythrocytes of all children were agglutinated by the maximum concentration (16 HAU) of adhesins A, B, and C: moreover 20% of them responded to a concentration of 4 HAU of adhesin A (index of adhesion: 0.25), 60% to 8 HAU of adhesin B (index of adhesion: 0.12), and 20% to 8 HAU of adhesin C *(table IV)*. The range of variability in the third week of life consists of 4 for adhesin A and 2 for adhesins B and C.

There was a reduction in the proportion with low indices of adhesion and an increase in the proportion of persons with higher parameters of adhesiveness observed in the subsequent development. The indices of adhesive ability of the children increased sharply, especially during the first three months of life. Thus the susceptibility of erythrocytes to the adhesion of meningococci serogroups A, B and C at first (up to 3 months) sharply and then slowly increases *(table IV)*.

During the second to fourth weeks after birth, the interaction with the same adhesins showed a decrease in the lower indices of adhesion and corresponding increase in the frequency of higher levels. In all other age groups both high and low indices of individual sensitivity to adhesion were revealed. In the period of 1–3 months of age erythrocytes of most children have reached a level of

Table III. Sensitivity of women during pregnancy and childbirth to adhesion of *N. meningitidis.*

Meningococci	*Number of individuals tested*	*Indices of adhesion and their incidence (%)*					
		0.06	*0.12*	*0.25*	*0.5*	*1.0*	*2.0*
During pregnancy (17–36 weeks)							
A	11	0	0	9	55	36	0
B	11	0	0	9	45	45	0
C	11	0	9	18	64	9	0
During childbirth							
A	11	0	9	18	9	64	0
B	11	9	0	27	36	27	0
C	11	9	9	18	18	27	0

Table IV. Ontogenesis of childrens' erythrocyte sensitivity to adhesion of *N. meningitidis* groups A, B and C.

Meningococci	*Number of individuals tested*	*Incidence of indices of adhesion (%)*						*Range of individual distinctions*
		0.06	0.12	0.25	0.5	1.0	2.0	
1st week								
A	103	0	0	0	0	0	0	–
B	103	0	0	0	0	0	0	–
C	103	0	0	0	0	0	0	–
2nd week								
A	6	83	17	0	0	0	0	2
B	6	0	0	0	0	0	0	–
C	6	0	0	0	0	0	0	–
3rd week								
A	5	80	0	20	0	0	0	4
B	5	40	60	0	0	0	0	2
C	5	80	20	0	0	0	0	2
4th week								
A	9	56	11	22	11	0	0	8
B	9	22	56	0	22	0	0	8
C	9	78	11	11	0	0	0	4
2nd-3rd months								
A	19	32	42	26	0	0	0	4
B	19	47	21	21	11	0	0	8
C	19	74	21	5	0	0	0	4
4th-12th months								
A	23	4	48	14	17	17	0	16
B	23	13	39	26	13	9	0	16
C	23	26	56	0	4	14	0	16
2nd-3rd years								
A	44	7	32	34	20	7	0	16
B	44	14	50	25	11	0	0	16
C	44	9	43	30	14	4	0	16

adhesion equal to 0.12–0.25. None of the samples from the 1 to 3-month age group had indices of adhesion equal to 1 and 2. The range of individual variation reached the value of 16 only after three months of life. The erythrocytes of some children were agglutinated by all of the adhesins tested (A, B and C); others were sensitive to one or two.

In the 4 to 12-month age the range of distinctions consisted of more than 16 times, and 47% of the samples had indices of adhesion equal to 0.25–1. The maximum index of adhesion (two or more) was found only in adults (18–60 years). Amongst 209 children examined during their first three years, there were no individuals with a high index of adhesion (2.0). Among 137 adults, there were 11 (8%) samples of erythrocytes with high indices of sensitivity. In another adult group of 5 149 young men, 47% demonstrated indices of adhesion of two or more. Thus during the postnatal period of ontogenesis the cells become either high or low in individual sensitivity to meningococcal adhesion.

4. Discussion

There are striking differences in the agglutinability of erythrocytes from animals, neonates, older children and adults by adhesive preparations from meningococci. Of twelve erythrocyte species tested, only human cells interacted with *N. meningitidis* adhesines, and the cells of

Table V. Diversity of newborn children and adults in sensitivity to adhesion of influenza viruses types A and B.

Types of influenza viruses	*Newborn children*						*Adults*					
	Number of individuals tested	*Indices of adhesion and their incidence(%)*					*Number of individuals tested*	*Indices of adhesion and their incidence (%)*				
		0.12	*0.25*	*0.5*	*1.0*	*2.0*		*0.12*	*0.25*	*0.5*	*1.0*	*2.0*
A	20	–	25	45	30	0	29	0	21	72	7	0
B	20	–	20	50	30	0	29	0	38	59	3	0

various individuals reacted differently. The number of erythrocyte specimens agglutinated by the meningococcal adhesins increased during postnatal ontogenesis and then was comparatively stable.

The lack of agglutination of animal erythrocytes by meningococcal adhesins correlated with natural immunity of animals' *N. meningitidis* infection. Evidence of the weak adhesive interaction of *N. meningitidis* with red blood cells correlates with low level of meningococcal infection among newborn infants and children under one month.

In older age groups there was agglutination of erythrocytes by the meningococcal adhesins, but among some individuals only. The range of individual diversity increased from absolute absence in one-week-old children up to maximal values (128 times) in adults. The maximum agglutination by *N. meningitidis* occurred only with cells of some but not all of the individuals tested. The adhesion of meningococci serogroups A, B and C to human red blood cells is individual and age dependent.

There is epidemiological and clinical evidence that different persons have different susceptibility to *N. meningitidis* as well as severity of disease. Variation in agglutination of erythrocytes of individuals by meningococcal adhesins needs to be examined in relation to susceptibility and severity of meningococcal disease. Lack of agglutination of red cells by meningococcal adhesins among species in which the disease does not occur indicates this might be a marker of natural immunity to this pathogen. In view of the above data it does not seem surprising that erythrocytes from different persons showed impressive differences in their capacity to adhere *N. meningitidis*. We can therefore hypothesise that resistance of erythrocytes from some individuals to adhesion of meningococci may correlate with their individual resistance to *N. meningitidis* infection. The discussed form of human individuality can explain why meningococcal disease develops in only a small proportion of individuals carrying the causative bacteria.

Thus, evidence that resistance of cells to adhesion of meningococci correlates with resistance of the whole body to infection is provided by the aggregate of facts that all categories of organisms known to be resistant to natural infection consist of cells insensitive to adhesion. In contrast, the organisms known to be susceptible to natural infection contain susceptible cells. At this stage of investigation evidence of the correlation between the tested organism's adhesive potency and its resistance to meningococcal infection is provided by the fact that all species and human age categories considered to be resistant to infection are resistant to adhesion too. The next step should be realised by investigation of persons affected by various forms of meningococcal infection.

From these data one could infer that specific function of meningococcal adhesin receptors do not exist in erythrocyte plasma membrane of resistant animals and children under one month. On the other hand, these receptors may be present either in various amounts, or have various activity, or a different location or another structure in the erythrocyte plasma membranes of some children over one month and some adults.

In contrast, the erythrocytes of the same newborns as well as those of adults can adhere to influenza virus types A and B, although with individually different intensity. In line with these results, it is well known that children under one month can fall ill with influenza infection relatively often. These results could be interpreted as meaning that influenza virus receptors are present at the human cell at the moment of birth, whereas the receptors of *N. meningitidis* adhesion develop later in the course of ontogenesis than those of influenza viruses.

The above results suggest that different receptor structures are involved in the interaction of human cells with influenza viruses and meningococci and the function of meningococcal reception on human cells develops during postnatal ontogenesis. Meanwhile, pregnancy and childbirth had no influence on the level of women's cell sensitivity to adhesion of *N. meningitidis*.

If the actual physiological function of pathogenic microbe receptors is the reception of specific molecular cytoecological agents, for example hormones, mediators, or chalones [8, 9], that gives the basis to suggest that the ontogenesis of cell sensitivity to adhesion of meningococci reflects certain stages of the receptors' physiological ripening. A probable factor involved in such a phenomenon may be that the young erythrocytes or resistant cells of some older individuals contain fewer receptors in their membrane than the sensitive cells.

The nonsensitivity of erythrocytes from other species to adhesion of *N. meningitidis* indicates that some cell surface molecules unique to cells of some humans could act as receptors. Human blood antigens present one such group of cell surface biomolecules. On the other hand, the adherence of *N. meningitidis* to cell surfaces involves lectin-like sites on the microbial surface which bind to specific ganglioside radicals on affected cells. This concept was illustrated by the ganglioside-inhibited binding of meningococcus to erythrocytes as well as to epitheliocytes and leukocytes [16]. According to data obtained it is becoming increasingly clear that certain peculiarities of the molecular constitution of cells can contribute to whether or not a child or adult will develop meningococcal infection. Revealing the age and individual distinctions is the first step to decoding their molecular basis.

Thus, the phenomenon of newborns' resistance to meningococcal infection may be associated with some constitutional peculiarities of the age of the organism, namely with impotence of cellular receptor structures, responsible for the agent adhesion that is the key stage of the infectious process. The spectrum of disease incidence and severity in *N. meningitidis* meningitis also can be attributed to the heterogeneity of human populations' susceptibility of cells to adhesion of the infectious agent. The conjoint effects of the victims' ontogenesis and subsequent heterogeneity in the ability of their cells in the adhesion of *N. meningitidis* can help explain some intriguing epidemiological and clinical observations. However, extended investigations at the level of individuals are necessary in order to draw comprehensive conclusions. Whether an individual infected with *N. meningitidis* will develop disease or not will depend on a variety of risk factors. Certainly, adhesive ability of the victim's cells is one of them. The second,

third and other factors could be found in transmembrane and intracellular stages of pathogenesis.

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