Pastorex™ Meningitis

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REF 61607	REF 61611	REF 61616
REF 61608	REF 61613	REF 61618
REF 61610	REF 61614	

Agglutination test for the qualitative detection of soluble antigens of *Neisseria meningitidis* groups A, C, Y/W135 and B/*E. coli* K1; *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and group B *Streptococcus* in cerebrospinal fluid and blood cultures; and for the identification of *Neisseria meningitidis* groups A, C, and B/*E. coli* K1; *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Streptococcus* group B from isolated colonies on agar culture media.

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Table of Content

1. INTENDED USE

Pastorex™ Meningitis assay is an agglutination test intended for the rapid diagnosis of bacterial meningitis by:

- The qualitative detection of soluble antigens to *Neisseria meningitidis* groups A, B/*E. coli* K1, C, Y/W135, *Haemophilus influenzae* type b, *Streptococcus pneumoniae* and group B *Streptococcus*, in cerebrospinal fluid (CSF) and blood cultures;
- The identification of *Neisseria meningitidis* groups A, B/*E. coli* K1 and C; *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and group B *Streptococcus* from suspected colonies isolated on agar culture media.

2. SUMMARY AND EXPLANATION OF THE TEST

In spite of the progress realized in the diagnosis and the treatment of the infections, the bacterial meningitis remains an important cause of mortality and morbidity. A fast and precise diagnosis of the etiologic agent is major for the medical care and the implementation of an appropriate treatment [1, 2, 3].

Streptococcus pneumoniae, *Neisseria meningitidis*, *Haemophilus influenzae* b have been reported as the main causative organisms responsible for bacterial meningitis [4]. Group B *Streptococcus* [5] and *Escherichia coli* K1 [6, 7] are the major bacterial pathogens responsible for *meningitis* in newborns and premature infants. The polysaccharide antigen specific for *N. meningitidis* group B is identical to a polysaccharide antigen found with *E. coli* K1, which then permits the diagnosis of *E. coli* meningitis in newborns, of which about 80% are of the K1 strain [6]. *Streptococcus pneumoniae* [8] and *Neisseria meningitidis* are the major pathogens in children and adults. The infections due to *Haemophilus influenzae* b tend to disappear in Europe since the implementation of systematic vaccination [2].

An early diagnosis allows a fast therapeutic management and the implementation of preventive measures [9, 10]. The essential examination is still the CSF analysis [10]. Gram staining highlights bacteria identification in 50 to 80% of cases and the culture is positive in approx. 80% of the CSF samples. However, in case of early treatment, the sensitivity of these two tests is lower than 50% [2, 3].

The conventional technique of bacterial identification by culture, while essential for susceptibility testing and confirmation of diagnosis, requires 18-24 hours, which is inadequate for emergency care. Moreover, false negative results can occur if the specimen has been transported and stored under unsatisfactory conditions, or if an antibiotic therapy has been initiated before the specimen was taken [9, 10, 11].

Thus, immunological techniques such as latex particle agglutination techniques for detecting soluble antigens released by the causative organisms into biological fluids, allow a more rapid diagnosis, in particular in the CSF during infection [12, 13]. Pastorex™ Meningitis assay is a simple test, requiring basic laboratory equipment and is easy to perform, allowing detection of serogroups of bacteria responsible for meningitis within only a few minutes [14, 15, 16]. Its convenience has been demonstrated in cases of outbreaks, to decide the appropriate vaccine to prescribe [10, 13, 14, 15, 16, 17].

3. PRINCIPLES OF THE PROCEDURE

Pastorex™ Meningitis assay is based on latex particle agglutination using visual interpretation. Polysaccharide antigens specific to the bacteria responsible for meningitis are detected using colored latex particles coated with strain-specific antibodies. Reaction in the presence of these specific antigens results in visible colored clumping of latex particles. In the absence of antigens, the latex particles remain in a homogenous suspension.

4. REAGENTS

4.1. DESCRIPTION

a) Pastorex™ Meningitis kit, code 61607 (25 tests):

Identification		Description	Presentation
R1	*N. meningitidis* B/ *E. coli* K1 Latex	**Red latex** suspension sensitized with mouse monoclonal antibody specific for *N. meningitidis* group B/*E. coli* K1 Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0,40 ml 1 **white cap** dropper bottle, **ready to use**
R2	*N. meningitidis* B/ *E. coli* K1 Negative control Latex	**Red latex** suspension sensitized with mouse monoclonal antibody specific for tetanus toxoid Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0,40 ml 1 **transparent cap** dropper bottle, **ready to use**
R3	*H. influenzae* b Latex	**White latex** suspension sensitized with rabbit antibodies specific for *H. influenzae* b Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml 1 **orange cap** dropper bottle, **ready to use**
R4	*S. pneumoniae* Latex	**Green latex** suspension sensitized with rabbit antibodies specific for *S. pneumoniae*. Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml 1 **green cap** dropper bottle, **ready to use**

Identification		Description	Presentation
R5	*Streptococcus* B Latex	**Yellow latex** suspension sensitized with rabbit antibodies specific for *Streptococcus* group B Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml 1 **yellow cap** dropper bottle, **ready to use**
R6	*N. meningitidis* A Latex	**Blue latex** suspension sensitized with rabbit antibodies specific for *N. meningitidis* group A Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml 1 **blue cap** dropper bottle, **ready to use**
R7	*N. meningitidis* C Latex	**Red latex** suspension sensitized with rabbit antibodies specific for *N. meningitidis* group C Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml 1 **red ca**p dropper bottle, **ready to use**
R8	*N. meningitidis* Y/ W135 Latex	**Pink latex** suspension sensitized with rabbit antibodies specific for *N. meningitidis* Y/W135 Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml 1 **plum cap** dropper bottle, **ready to use**
R9	Negative polyvalent control Latex	**Plum latex** suspension sensitized with IgG immunoglobulins from non-immunized rabbit Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml 1 **transparent cap** dropper bottle, **ready to use**
R10	Positive polyvalent control Antigenic extract	**Antigenic extract** containing the polysaccharide antigens of *N. meningitidis* A, C, B, Y/W135, *H. influenzae* b, group B *Streptococcus*, and *S. pneumoniae*. Preservative: 0.01% Bronidox	**1 bottle of freeze-dried** antigenic extract to be reconstituted with 1.0 ml sterile water (Volume sufficient for 18 reactions)
-	Cards	Disposable agglutination cards (9 circles, each identified for its latex reagent)	**30 units**
-	Sticks	Disposable mixing sticks	**3 x 100 units**

b) Pastorex™ Meningitis, individual latex tests (25 tests each):

Product code	Identification		Description	Presentation
61611	R1	*N. meningitidis* B/*E. coli* K1 Latex	**Red latex** suspension sensitized with mouse monoclonal antibody specific for *N. meningitidis* group B/*E. coli* K1 Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0,40 ml x 1 **white cap** dropper bottle, **ready to use**
61616	R3	*H. influenzae* b Latex	**White latex** suspension sensitized with rabbit antibodies specific for *H. influenzae* b Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml x 1 **orange cap** dropper bottle, **ready to use**
61614	R4	*S. pneumoniae* Latex	**Green latex** suspension sensitized with rabbit antibodies specific for *S. pneumoniae* Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml x 1 **green cap** dropper bottle, **ready to use**
61613	R5	*Streptococcus* B Latex	**Yellow latex** suspension sensitized with rabbit antibodies specific for group B *Streptococcus* Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml x 1 **yellow cap** dropper bottle, **ready to use**
61608	R6	*N. meningitidis* A Latex	**Blue latex** suspension sensitized with rabbit antibodies specific for *N. meningitidis* group A Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml x 1 **blue cap** dropper bottle, **ready to use**
61610	R7	*N. meningitidis* C Latex	**Red latex** suspension sensitized with rabbit antibodies specific for *N. meningitidis* group C Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	0.40 ml x 1 **red cap** dropper bottle, **ready to use**

c) Pastorex™ Meningitis Control kit, code 61618, for single latex test (for 2 x 25 tests):

Identification		Description	Presentation
R2	*N. meningitidis* B/ *E. coli* K1 Negative control Latex	**Red latex** suspension sensitized with mouse monoclonal antibody specific for tetanus toxoid Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	2 x 0,40 ml 2 **transparent cap** dropper bottle, **ready to use**
R9	Negative polyvalent control Latex	**Plum latex** suspension sensitized with IgG immunoglobulins from non-immunized rabbit Preservative: 0.3% ProClin™ 300 and 0.005% Gentamicin sulfate	2 x 0.40 ml 2 **transparent cap** dropper bottle, **ready to use**
R10	Positive polyvalent control Antigenic extract	**Antigenic extract** containing the polysaccharide antigens of *N. meningitidis* A, C, B, Y/W135, *H. influenzae* b, *Streptococcus* B, and *S. pneumoniae.* Preservative: 0.01% Bronidox	**2 bottles of freeze dried** antigenic extract to be reconstituted with 1.0 ml sterile water (Volume sufficient for **18** reactions)
-	Cards	Disposable agglutination cards (9 circles, each identified for its latex reagent)	**2 x 20 cards**
-	Sticks	Disposable mixing sticks	**2 x 100 sticks**

4.2. STORAGE AND HANDLING REQUIREMENTS

- Reagents can be used until the expiry date stated on the package if stored at +2-8°C and in the absence of microbial contamination (even once open).
- THE LATEX REAGENTS MUST NOT BE FROZEN.
- Ensure that the caps of the dropper bottles are firmly tightened to avoid contamination or drying of the reagents.
- Store the latex reagent bottles upright (inside the original foam provided in the kit).

Identification	Preservation (after first opening)
R1, R2, R3, R4, R5, R6, R7, R8, R9	After first opening: until the expiry date stated on the package at +2-8°C.
R10	After reconstitution: 1 month at +2-8°C; or until the expiry date when frozen at -20°C (do not refreeze once thawed)

5. WARNING AND PRECAUTIONS

For *in vitro* diagnostic use. For healthcare professional use.

5.1. HEALTH AND SAFETY PRECAUTIONS

- This test kit should be handled only by qualified personnel trained in laboratory procedures and familiar with their potential hazards. Wear appropriate protective clothing, gloves and eye/face protection and handle appropriately with the requisite Good Laboratory Practices.
- Dispose of all specimens and material used to perform the test as though they contain an infectious agent. Laboratory, chemical or bio-hazardous wastes must be handled and discarded in accordance with all local, regional and national regulations.
- For hazard and precaution recommendations related to some chemical components in this test kit, please refer to the pictogram(s) mentioned on the labels and the information supplied at the end of instruction for use. The Safety Data Sheet is available on www.biorad.com.

5.2. PRECAUTIONS RELATIVE TO THE PROCEDURE

5.2.1. Preparing

- In case of use of a routine lab orbital rotator different from the example mentioned in §7.2, the optimal speed must be carefully adjusted with the R10 reagent, to ensure homogenous agglutination on the whole circles surface. **Manual agitation is not recommended**.
- Do avoid drying of reagents deposited on the agglutination card(s) during the period of rotation; ensure that the orbital rotator is not placed under an air-conditioning flow.

- In case of use of a water-bath to heat the CSF samples at 100°C or a dry incubator, ensure that 100°C is reached inside the tube.
- Before use, wait for 10 minutes for the reagents to reach room temperature (18-25°C).
- It is recommended to rank the latex reagents following the card distribution pattern.
- Do not touch the reaction surface of the agglutination cards.
- The R10 reagent should be reconstituted with distilled sterile water avoiding any contamination.
- Use the plastic mixing sticks supplied in the kit for mixing the reagents with specimens or bacterial colonies.
- Do not use expired reagents.

5.2.2. Processing

- Perform the test at room temperature (between 18 - 25°C). Be sure any 100°C heated-CSF specimens are returned to room temperature before testing.
- In case of use of a water-bath to heat the CSF samples at 100°C, use watertight tubes to keep water from entering the tubes. Using a dry incubator is preferred. Shake gently the reagents before each use. Then check that the latex suspension remains homogenous before use.
- To ensure proper drop delivery, always hold the reagent dropper bottles in vertical position.
- Wipe the tip of the reagent in order to obtain a well calibrated drop.
- Change the mixing stick for each reaction.
- Discard all disposable material used in an autoclavable waste bin or disinfectant bath.

6. SPECIMENS

- Cerebrospinal fluid specimens: CSF samples should be treated as soon as possible after collection. If this is not possible, they can be stored up to four hours between +2 and +8°C. Bacteriological examinations (culture) should be performed as a matter of priority in order to avoid contamination of the sample. The minimal volume of sample for testing with the Pastorex™ Meningitis assay is 500 µl.

  No interference has been shown in CSF samples containing abnormal level of hemoglobin concentration (up to 2 mg/mL to mimick hemolysis).
- Positive blood culture: Samples should be treated immediately. Some blood culture media can result in non-specific reactions or misinterpretation. To anticipate such situations, it is recommended to test a negative control, using a blood culture inoculated with sterile blood or with a different organism other than those detected by Pastorex™ Meningitis assay.

- Bacterial grouping from isolated colonies: The test must be performed with fresh and well isolated colonies on agar culture media.

7. PROCEDURE

7.1. MATERIAL REQUIRED

- All materials listed in under “Reagents” and their controls
- Disposable agglutination test cards
- Disposable mixing sticks

7.2. MATERIAL REQUIRED BUT NOT PROVIDED

- Standard micropipette for distributing 30 and 50 µl
- Calibrated loops 1 µl and 5 µl for bacterial grouping
- Sterile distilled water
- Sterile physiological water
- Todd Hewitt broth **(code 55704)**
- Antiserum *Neisseria meningitidis* Y, W135, 29E Kit **(code 58704)**
- Watertight tubes
- Dry incubator or boiling water-bath at 100°C for the CSF assay procedure
- Orbital type rotator (i.e. speed 120 RPM using IKA model KS260 basic)
- Centrifuge for micro-tubes
- Timer
- Disinfectant bath

7.3. CSF ASSAY PROCEDURE

CSF specimen preparation:

- If the CSF is very turbid or contains red blood cells, centrifuge it for 5 minutes at 350 g and collect the supernatant.
- Heat all CSF samples for 3 minutes at 100°C. Ensure the sample temperature reaches the room temperature

(18-25°C) and then perform centrifugation for 5 minutes at 3,000 g.

CSF test procedure:

- Dispense 50 µl of the pre-treated sample supernatant in each circle of the agglutination card.
- Gently shake the latex reagents.
- Holding the dropper bottle upright, place one drop of each latex reagent on the disposable card following the indicated distribution pattern: R9, R6, R7, R1 and R2 in the white circles, and R8, R3, R4 and R5 in the black circles.

- Mix the latex reagents and the sample using a stick on the whole circle surface; change the stick between each latex reagent. Rotate the card gently (Cf. §5.2.1.) for 10 minutes.
- Observe for any agglutination visible to the naked eye within maximum **10 minutes**. Wait for the end of those 10 minutes to conclude a negative result.

7.4. BLOOD CULTURE PROCEDURE

Blood culture preparation:

- For presumptive orientation check the bacterial morphology and the Gram stain.
- Take 1 to 2 ml of a positive blood culture sample.
- Centrifuge for 5 minutes at 2,000 g.

Blood culture test procedure:

- Dispense 50 µl of supernatant in each circle on the disposable card, corresponding to the latex reagents to be tested, according to the Gram stain.
- Gently shake the latex reagents selected for the test.
- Holding the dropper bottle upright, place one drop of each selected latex reagent on the disposable card.
- Mix the latex reagents and the sample using a stick on the whole circle surface, change the stick between each latex reagent. Rotate the card gently (Cf. §5.2.1.) for **5 minutes**.
- Observe for any agglutination visible to the naked eye within maximum 5 minutes. Wait for the end of those 5 minutes to conclude a negative result.

7.5. ISOLATED BACTERIAL STRAINS GROUPING PROCEDURE

Prior to performing the test, check the morphology and Gram stain for a presumptive bacterial orientation:

Gram and Morphology	Orientation test	Presumptive bacterial identification
Gram-negative bacteria	Oxidase test	(+): *Neisseria meningitidis*, *Haemophilus influenzae* b
		(-): *Escherichia coli* K1
Gram-positive cocci	Catalase test	(+): Do not test these colonies
		(-): *Streptococcus pneumoniae**, group B *Streptococcus*

** Non-encapsulated S. pneumoniae strains cannot be identified by immuno-agglutination latex [8].*

a) N. meningitidis (A, B, and C only), H. influenzae b, E. coli K1, S. pneumoniae

***N. meningitidis* Y/W135 Latex reagent (R8) cannot be used for grouping of bacterial strains isolated on agar culture media**. To determine these groups, it is recommended to use conventional antisera (Bio-Rad Antiserum Neisseria meningitidis Y, W135, 29E Kit, code 58704).

- Dispense 30 µl of sterile physiological solution in the circle on the disposable card.
- Sample preparation:
  - *N. meningitidis*, *H. influenzae* b and *E. coli* K1: the equivalent of 1 µl loop, which corresponds to 2 to 3 colonies.
  - *S. pneumoniae*: the equivalent of 5 µl loop, which corresponds to a **minimum** of 10 to 12 colonies.
- Carefully emulsify the sampled colonies with the loop in such a way in order to obtain a homogeneous suspension.
- Gently shake, the reagent(s) chosen for identification; holding the dropper bottle(s) upright, place one drop of the appropriate R1, R3, R4, R6 or R7 reagent(s) at the periphery of the bacterial suspension on the disposable card.
- Mix the drop of latex and the sample suspension using a stick.
- Rotate the card gently (Cf. §5.2.1.).
- Observe for any agglutination visible to the naked eye within a **maximum of 2 minutes**. Wait for the end of those 2 minutes to conclude a negative result.
- Confirm the identification of the species using conventional biochemical testing.

b) Group B Streptococcus (ß-hemolytic colonies)

- Using a 5 µl loop, suspend 7 to 8 colonies in 3 ml of a Todd Hewitt broth (code 55704).
- Incubate in 37°C water-bath for 2 to 3 hours.
- Centrifuge 5 minutes at 3,000 g.
- Dispense 50 µl of supernatant in the corresponding circle of the disposable card.
- Gently shake the R5 reagent; holding the dropper bottle upright, place one drop at the periphery of the bacterial suspension.
- Mix the drop of latex and the sample using a stick.
- Rotate the card gently (Cf. §5.2.1.). Observe for any agglutination visible to the naked eye **in less than 1 minute**.
- Confirm identification of the species using conventional biochemical tests.

7.6. QUALITY CONTROL

The latex reagents should be completely homogenous after shaking.

- Dispense 50 µl of the **Positive polyvalent control Latex (R10)** in each circle on the disposable card.
- Gently shake the latex reagents. Holding the dropper bottles upright, place one drop of each latex reagent on the disposable card following the indicated distribution pattern: R9, R6, R7, R1 and R2 reagents in the white circles; and R8, R3, R4 and R5 reagents in the black circles.
- Mix the latex reagents and the R10 reagent using a stick, changing the stick between each latex reagent.
- Rotate the card gently (Cf. §5.2.1.) **for 10 minutes**. During this 10 minute-period, observe for the appearance of any agglutination (compare the test latex reactions with those of the latex negative controls).
- Agglutination intensity and rate of appearance depend on antigen/antibody avidity. As a result, the reactions observed are variable for each latex reagent. Those of *N. meningitidis* B/*E.coli* K1 Latex (R1) are finer than those of the others.
- A sterile physiological water controls the absence of unspecific agglutination of each latex reagent. To perform this quality-control test, sterile physiological water is used according to the protocol for the Positive polyvalent control latex (Cf. aforementioned procedure).
- The latex reagents should not be used when they do not agglutinate with R10 reagent, or when they non-specifically agglutinate with sterile physiological water (this could be due to incorrect storage conditions of the kit or a latex reagent contamination).

7.7. INTERPRETATION OF THE RESULTS

Positive reaction

A positive reaction is indicated by fine agglutination, visible to the naked eye, compared to the R2 and R9 negative control latex. Agglutination intensity and time of appearance depends upon the concentration of antigen in the sample tested.

A discrepancy between a positive antigen test and a negative culture can be explained by the absence of viable bacteria in the cultured sample (antibiotic treatment started before the sample was taken or transport conditions not suited to the survival of fragile bacteria).

In most cases, a positive reaction with *N. meningitidis* B/*E.coli* K1 Latex (R1) in a new-born or premature infant indicates infection by E. coli K1. In an older subject, *N. meningitidis* B is more probable. Culture of the sample must confirm the diagnosis.

Negative reaction

A negative reaction is indicated by a homogenous suspension, without clumps.

Non-interpretable results

A reaction is un-interpretable if the sample agglutinates with the negative controls latex (R2 or R9 reagent) and/or with more than one latex reagent in the kit. In this case, it is recommended to repeat the test with another sample and wait for result of the culture. (Very rarely, an infection can be due to two different bacterial species).

8. TEST LIMITATION

- In numerous cases, immunologic latex technique allows a presumptive diagnosis of the organism. However, the antigen concentration in the sample may be below the lower limit of detection of the latex and produce a negative reaction. It can be useful in this case to repeat the sample at a later time.
- This technique cannot replace cultivation of the bacteria, which alone permits the establishment of an antimicrobial susceptibility result.
- Considering the wide variety of blood culture media, performances cannot be guaranteed for all media (Cf. §6).
- A few examples of unrelated bacteria possessing similar antigens have been reported. The possibility of cross-reactions should always be considered [18, 19, 20].
- ***N. meningitidis* Y/W135 Latex reagent (R8) cannot be used for grouping of bacterial strains isolated on agar culture media**. To determine these groups, it is recommended to use conventional antisera (Bio-Rad Antiserum *Neisseria meningitidis* Y, W135, 29E Kit, code 58704).
- The final diagnosis, as for all laboratory diagnoses, cannot be based on the results of one single test, but on an overview of the clinical data and the biochemical, cytological and immunological results.
- Soluble antigens detection in blood cultures, as well as grouping of strains isolated on agar culture media, should be completed by a species identification of the bacterial strain.

9. PERFORMANCES CHARACTERISTICS

9.1 PRECISION MEASUREMENT

A panel of 2 specimens was used for determining the reproducibility and precision of the Pastorex™ Meningitis assay. The 2-member precision panel included 1 negative (non-reactive with all latex reagents) and 1 multipositive composed of seven antigens weakly reactive with R1, R3 R4, R5, R6, R7 and R8, and non-reactive with R2 and R9 reagents.

9.1.1 Repeatability

Precision panel (N=2) was tested in replicates of 10 on the same day, on one lot of Pastorex™ Meningitis assay and read by one operator. Negative and positive panel members gave the same expected results with all the 10 replicates.

Table I: Repeatability results

Repeatability with Pastorex™ Meningitis assay		**Negative panel member**			**Multipositive panel member**		
Latex reagent	Strain detection	Total reps	Non-reactive	Reactive	Total reps	Non-reactive	Reactive
R1	***N. meningitidis*** **B/*E. coli*** **K1**	10	10	0	10	0	10
R2	***N. meningitidis*** **B/*E. coli*** **K1 (Negative control Latex)**	10	10	0	10	10*	0
R3	***H. influenzae*** **b**	10	10	0	10	0	10
R4	***S. pneumoniae***	10	10	0	10	0	10
R5	***Streptococcus*** **B**	10	10	0	10	0	10
R6	***N. meningitidis*** **A**	10	10	0	10	0	10
R7	***N. meningitidis*** **C**	10	10	0	10	0	10
R8	***N. meningitidis*** **Y/W135**	10	10	0	10	0	10
R9	**Negative polyvalent control Latex**	10	10	0	10	10*	0

Note: (*) = expected results (R2 and R9 are control latex beads)

9.1.2 Intermediate Precision

Precision panel (N=2) was tested in replicates of 20 by two independent operators in 2 replicates per day during

5 days. As shown on table VIII, negative and positive panel members gave the same expected results with all the 20 replicates.

Table II: Run-to-run, day-to-day and inter-operator precision results

Run and Day Precision with Pastorex™ Meningitis assay		**Negative panel member**			**Multipositive panel member**		
Latex reagent	Strain detection	Total reps	Non-reactive	Reactive	Total reps	Non-reactive	Reactive
R1	*N. meningitidis* B/*E. coli* K1	20	20	0	20	0	20
R2	*N. meningitidis* B/*E. coli* K1 **(Negative control Latex)**	20	20	0	20	20*	0
R3	*H. influenzae* b	20	20	0	20	0	20
R4	*S. pneumoniae*	20	20	0	20	0	20
R5	*Streptococcus* B	20	20	0	20	0	20
R6	*N. meningitidis* A	20	20	0	20	0	20
R7	*N. meningitidis* C	20	20	0	20	0	20
R8	*N. meningitidis* Y/W135	20	20	0	20	0	20
R9	**Negative polyvalent control Latex**	20	20	0	20	20*	0

Note: (*) = expected results (R2 and R9 reagents are control latex beads)

9.1.3 Inter-lot Precision

Inter-lot precision panel including reactive soluble meningeal antigenic solutions, reactive and non-reactive meningeal strains and two non-reactive reference cerebrospinal fluids, was tested on three lots of Pastorex™ Meningitis assay. As shown on table III of agglutination results, negative and positive panel members gave the same expected results with the three lots.

Table III: Inter-lot precision results

Inter-lot Precision with Pastorex™ Meningitis assay		**Agglutination Intensity (from 0 to 3)***											
		Soluble Antigens			**Strains Panel**			**Reference CSF-1**			**Reference CSF-2**		
Latex reagent	Strain detection	Lot 1	Lot 2	Lot 3	Lot 1	Lot 2	Lot 3	Lot 1	Lot 2	Lot 3	Lot 1	Lot 2	Lot 3
R1	*N. meningitidis* B	2.5-	2.5	2.5	3	3	3	0	0	0	0	0	0
	E. coli K1	nd			3	3	3						
R2	*N. meningitidis* B/ *E. coli* K1 **(Negative control Latex)**	0	0	0	0	0	0	0	0	0	0	0	0
R3	*H. influenzae* b	2.5	3	3	3	3	3	0	0	0	0	0	0
R4	*S. pneumoniae***	1.5	2	2	3	3	2.5	0	0	0	0	0	0
		3	3	3									
R5	*Streptococcus* B	2.5	2.5	2	3	3	3	0	0	0	0	0	0
	Streptococcus A	nd			0	0	0	nd					
	Streptococcus C				0	0	0						
	Streptococcus D				0	0	0						
	Streptococcus F1				0	0	0						
	Streptococcus G				0	0	0						
R6	*N. meningitidis* A	2	3	3	3	3	3	0	0	0	0	0	0
R7	*N. meningitidis* C	3-	3	3	3	3	3	0	0	0	0	0	0
R8	*N. meningitidis* Y	2.5	2.5	3	nd			0	0	0	0	0	0
	N. meningitidis W135	1.5	2.5	2.5				0	0	0	0	0	0
R9	**Negative polyvalent control Latex**	nd			0	0	0	0	0	0	0	0	0

Notes: nd = not determined; (*) Agglutination Intensity quotation was fine-tuned with .5 and + or – suffix (e.g 2.5+ is comprised between 2 and 3 and with slightly more intensity than 2.5-); (**) Two different Streptococcus pneumoniae (03 and 9V) soluble antigenic solutions have been tested with R4 reagent latex.

9.2 DIAGNOSTIC PERFORMANCES

9.2.1 Diagnostic Specificity

a) Specificity with CSF specimens

A maximum of 61 CSF sterile specimens known as negative were tested with the Pastorex™ Meningitis assay. All specimens tested negative with any of the latex reagents. Therefore, specificity of the Pastorex™ Meningitis assay is 100%. Some of these specimens were artificially contaminated with bacteria responsible for meningitis but different from those detected by the Pastorex™ Meningitis assay without giving impact on specificity that remained at 100%.

Table IV: Specificity with CSF

Specificity on CSF	Strain detection	Sterile CSF specimens			CSF specimens with bacterial contamination		
		Number tested	Number found non-reactive	Specificity (%)	Number tested	Number found non-reactive	Specificity (%)
R1	*N. meningitidis* B/*E. coli* K1	12	12	**100**	nd	nd	nd
R3	*H. influenzae* b	61	61	**100**	32	32	**100**
R4	*S. pneumoniae*	60	60	**100**	39	39	**100**

Specificity on CSF	Strain detection	Sterile CSF specimens			CSF specimens with bacterial contamination		
		Number tested	Number found non-reactive	Specificity (%)	Number tested	Number found non-reactive	Specificity (%)
R5	*Streptococcus* B	49	49	**100**	58	58	**100**
R6	*N. meningitidis* A	52	52	**100**	50	50	**100**
R7	*N. meningitidis* C	52	52	**100**	56	56	**100**
R8	*N. meningitidis* Y/W135	40	40	**100**	40	40	**100**

b) Specificity with colonies from bacterial culture

Specificity performance tested with R1 reagent on 53 strains belonging to genuses *Neisseria* (N=20 with *meningitidis* A, C, Y, W135 and others), *Branhamella* (N=1), *Acinetobacter* (N=5), *Klebsiella* (N=6), *Streptococcus* (N=7 with B, *pneumoniae* and others), *Haemophilus influenza* (N=6), *Serratia* (N=1 *marscesens*) and *Enterobacter aerugenes* (N=1), *Pseudomonas aeruginosa* (N=2), *Escherichia coli* non K1 (N=4) is 90.6% (48/53), showing some cross-reactivity. One false positive result was obtained with *Neisseria flavescens*, two false positive with *Klebsiella pneumoniae* and two false positive with *Acinetobacter haemolyticus* and *Acinetobacter baumanii* strains.

Specificity performance tested with R3 to R7 reagents on 330 strains belonging to genuses *Neisseria* (N≤109), *Branhamella* (N≤5), *Acinetobacter* (N≤6), *Streptococcus* (N≤11), *Klebsiella* (N≤3), *Haemophilus* (N≤10), *Escherichia coli* (N≤1), *Moraxella* (N≤3) and *Oligella* (N≤1) is 100%.

Table V: Specificity with colonies from bacterial culture

Specificity on colonies	Strain detection	Number tested	Number found non-reactive	Specificity (%)
R1	*N. meningitidis* B/*E. coli* K1	53	48 (*)	**90.6**
R3	*H. influenzae* b	31	31	**100**
R4	*S. pneumoniae*	33	33	**100**
R5	*Streptococcus* B	17	17	**100**
R6	*N. meningitidis* A	122	122	**100**
R7	*N. meningitidis* C	127	127	**100**

Note: (*) Cross-Reactivity with strains: One false positive result was obtained with Neisseria flavescens, two false positive with Klebsiella pneumoniae and two false positive with Acinetobacter haemolyticus and Acinetobacter baumanii strains.

c) Specificity with Blood Culture

Specificity performance tested with R1 reagent on 39 blood cultures with identified strains belonging to genuses *Acinetobacter* (N=2), *Candida* (N=1), *Klebsiella* (N=7), *Staphylococcus* (N=16), *Serratia* (N=1), *Micrococcus* (N=2), *Enterobacter* (N=3), and *Escherichia coli* (N=7) is 97.4% (38/39), showing minor cross-reactivity (one false positive result was obtained *Klebsiella pneumoniae* strains).

Specificity performance tested with R3 to R7 reagents on 37 blood culture specimens is 100%.

Table VI: Specificity with blood culture

Specificity on colonies	Strain detection	Number tested	Number found non-reactive	Specificity (%)
R1	*N. meningitidis* B/*E. coli* K1	39	38 (*)	**97.4**
R3	*H. influenzae* b	37	37	**100**
R4	*S. pneumoniae*	37	37	**100**
R5	*Streptococcus* B	37	37	**100**
R6	*N. meningitidis* A	37	37	**100**
R7	*N. meningitidis* C	37	37	**100**

Note: (*) Cross-reactivity: One false positive result was obtained with Klebsiella pneumoniae.

9.2.2 Diagnostic Sensitivity

a) Sensitivity with CSF specimens

Sensitivity performance tested on 77 positive CSF specimens was found between 91.7% and 100% according to the latex reagents.

Table VII: Sensitivity with CSF

Sensitivity on CSF	Strain detection	Number tested	Number found Reactive	Sensitivity (%)
R1	*N. meningitidis* B/ *E. coli* K1	3	3	**100**
R3	*H. influenzae* b	34	33	**97.1**
R4	*S. pneumoniae*	24	22	**91.7**
R5	*Streptococcus* B	1	1	**100**
R6	*N. meningitidis* A	12	12	**100**
R7	*N. meningitidis* C	3	3	**100**

b) Sensitivity with colonies from bacterial culture

Sensitivity performance tested on 95 strains is 100%.

Table VIII: Sensitivity with colonies from bacterial culture

Sensitivity on colonies	Strain detection	Number tested	Number found Reactive	Sensitivity (%)
R1	*N. meningitidis* B/*E. coli* K1	10 (*)	10	**100**
R3	*H. influenzae* b	17	17	**100**
R4	*S. pneumoniae*	15	15	**100**
R5	*Streptococcus* B	15	15	**100**
R6	*N. meningitidis* A	22	22	**100**
R7	*N. meningitidis* C	16	16	**100**

Note: (*) 10 strains (9 N. meningitidis and 1 E.coli K1) were tested with R1 latex.

c) Sensitivity with Blood culture

Sensitivity performance tested on 4 blood culture specimens with R4 (*S. pneumoniae* Latex) and R5 (*Streptococcus* B Latex) reagents is 100%.

Table IX: Sensitivity with blood culture

Sensitivity on blood culture	Strain detection	Number tested	Number found Reactive	Sensitivity (%)
R4	*S. pneumoniae*	2	2	**100**
R5	*Streptococcus* B	2	2	**100**

9.3 ANALYTICAL SENSITIVITY

Analytical sensitivity of Pastorex™ Meningitis assay was determined for each latex reagent using serial dilutions of corresponding meningeal antigens of known concentrations until absence of detection. Table X summarizes the lowest detectable concentration found for each Pastorex™ latex reagents.

Table X: Analytical sensitivity of Pastorex™ Meningitis assay

Latex Reagent	Strain detection	Sensitivity threshold
R1	*N. meningitidis* B/*E. coli* K1	**62.5**
R3	*H. influenzae* b	**0.1**
R4	*S. pneumoniae*	**95**
R5	*Streptococcus* B	**20**
R6	*N. meningitidis* A	**2.5**
R7	*N. meningitidis* C	**2.5**
R8	*N. meningitidis* Y	**5.0**
	N. meningitidis W135	**2.5**

9.4 ANALYTICAL SPECIFICITY/CROSS REACTIVITY

See §9.2.1 Diagnostic specificity with blood culture or colonies from bacterial culture.

9.5 HOOK EFFECT

The existence of a possible hook effect was studied by testing negative artificial CSF samples with antigenic solution at 100 µg/ml as high titer sample, at different dilutions. The equivalence of results observed among non-diluted and diluted samples indicates the absence of the hook effect on the samples tested.

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(CZ) • Tento výrobek obsahuje lidské nebo zvířecí komponenty. Zacházejte s ním opatrně.
(DE) • Dieses Produkt enthält Bestandteile menschlichen oder tierischen Ursprungs. Vorsichtig handhaben.
(DK) • Dette produkt indeholder humane og animalske komponenter. Skal behandles med forsigtighed.
(EE) • Käesolev toode sisaldab inim-või loomseid komponente. Käsitseda ettevaatlikult.
(EN) • This product contains human or animal components. Handle with care.
(ES) • Este producto contiene componentes humanos o animales. Manejar con cuidado.
(FI) • Tässä tuotteessa on ihmisestä tai eläimistä peräisin olevia osia. Käsittele varovasti.
(FR) • Ce produit contient des composants d'origine humaine ou animale. Manipuler avec précaution.
(GR) • Αυτό το προϊόν περιέχει ανθρώπινα ή ζωικά στοιχεία. Χειριστείτε το με προσοχή.
(HR) • Ovaj proizvod sadrži ljudske ili životinjske sastojke. Pažljivo rukovati.
(HU) • A készítmény emberi vagy állati eredetű összetevőket tartalmaz. Óvatosan kezelendő.
(IT) • Questo prodotto contiene componenti umane o animali. Maneggiare con cura.
(LT) • Šiame produkte yra žmogiškosios arba gyvūninės kilmės sudėtinių dalių. Elgtis atsargiai.
(LV) • Šis produkts satur cilvēkiem vai dzīvniekiem paredzētas sastāvdaļas. Apieties uzmanīgi.
(NL) • Dit product bevat menselijke of dierlijke bestanddelen. Breekbaar.
(NO) • Dette produktet inneholder humane eller animalske komponenter. Håndteres med forsiktighet.
(PL) • Niniejszy produkt zawiera składniki pochodzenia ludzkiego lub zwierzęcego. Należy obchodzić się z nim ostrożnie.
(PT) • Este medicamento contém componentes de origem humana ou animal. Manuseie com cuidado.
(RO) • Acest produs conține materiale de origine umană sau animală. Manevrați-l cu grijă.
(SE) • Denna produkt innehåller beståndsdelar från människa eller djur. Hantera produkten varsamt.
(SI) • Izdelek vsebuje človeške ali živalske sestavine. Rokujte previdno.
(SK) • Tento výrobok obsahuje ľudské alebo zvieracie zložky. Narábajte s ním opatrne.

H317
P280-P302+P352-
P333+P313-P501

(BG)
внимание
Може да причини алергична кожна реакция.
Използвайте предпазни ръкавици/предпазно облекло/предпазни очила/предпазна маска за лице. ПРИ КОНТАКТ С КОЖАТА: Измийте обилно със сапун и вода. При поява на кожно дразнене или обрив на кожата: Потърсете медицински съвет/помощ. Изхвърлете съдържанието/контейнера в съответствие с местните/регионалните/националните/международните разпоредби.

(CZ)
Varování
Může vyvolat alergickou kožní reakci.
Používejte ochranné rukavice/ochranný oděv/ochranné brýle/obličejový štít. PŘI STYKU S KŮŽÍ: Omyjte velkým množstvím vody a mýdla. Při podráždění kůže nebo vyrážce: Vyhledejte lékařskou pomoc/ošetření. Obsah/nádobu likvidujte v souladu s místními/regionálními/národními/mezinárodními předpisy.

(DE)
Achtung
Kann allergische Hautreaktionen verursachen.
Schutzhandschuhe/Schutzkleidung/Augenschutz/Gesichtsschutz tragen. BEI KONTAKT MIT DER HAUT: Mit viel Wasser und Seife waschen. Bei Hautreizung oder -ausschlag: Ärztlichen Rat einholen/ärztliche Hilfe hinzuziehen. Entsorgung des Inhalts / des Behälters gemäß den örtlichen / regionalen / nationalen/ internationalen Vorschriften.

(DK)
Advarsel
Kan forårsage allergisk hudreaktion.
Bær beskyttelseshandsker/beskyttelsestøj/øjenbeskyttelse/ansigtsbeskyttelse VED KONTAKT MED HUDEN: Vask med rigeligt sæbe og vand. Ved hudirritation eller udslet: Søg lægehjælp. Bortskaffelse af indholdet/beholderen i henhold til de lokale/regionale/nationale/internationale forskrifter.

(EE)
Hoiatus
Võib põhjustada allergilist nahareaktsiooni.
Kanda kaitsekindaid/kaitserõivastust/kaitseprille/kaitsemaski. NAHALE SATTUMISE KORRAL: pesta rohke vee ja seebiga. Nahaärrituse või _obe korral: pöörduda arsti poole. Sisu/konteineri kāitlus vastavuses kohalike/regionaalsete/rahvuslike/rahvusvaheliste nõuetega.

(EN)
Warning
May cause an allergic skin reaction.
Wear protective gloves/protective clothing/eye protection/face protection. IF ON SKIN: Wash with plenty of soap and water. If skin irritation or rash occurs: Get medical advice/attention. Dispose of contents/container in accordance with local/regional/national/international regulations.

(ES)
Atención
Puede provocar una reacción alérgica en la piel.
Llevar guantes que aíslen del frío/gafas/máscara.
EN CASO DE CONTACTO CON LA PIEL: Lavar con agua y jabón abundantes. En caso de irritación o erupción cutánea: Consultar a un médico. Eliminar el contenido o el recipiente conforme a la reglamentación local/regional/nacional/internacional.

(FI)
Varoitus
Voi aiheuttaa allergisen ihoreaktion.
Käytä suojakäsineitä/suojavaatetusta/silmiensuojainta/kasvonsuojainta. JOS KEMIKAALIA JOUTUU IHOLLE: Pese runsaalla vedellä ja saippualla. Jos ilmenee ihoärsytystä tai ihottumaa: Hakeudu lääkäriin. Säilytä säiliö(t) noudattaen paikallisia/alueellisia/kansallisia/kansainvälisiä määräyksiä.

(FR)
Attention
Peut provoquer une allergie cutanée.
Porter des gants de protection/des vêtements de protection/un équipement de protection des yeux/du visage. EN CAS DE CONTACT AVEC LA PEAU: laver abondamment à l'eau et au savon. En cas d'irritation ou d'éruption cutanée: consulter un médecin. Éliminer le contenu/récipient conformément à la réglementation locale/régionale/nationale/internationale.

(GR)
Προσοχή
Μπορεί να προκαλέσει αλλεργική δερματική αντίδραση.
Να φοράτε προστατευτικά γάντια/προστατευτικά ενδύματα/μέσα ατομικής προστασίας για ταμάτια/πρόσωπο. ΣΕ ΠΕΡΙΠΤΩΣΗ ΕΠΑΦΗΣ ΜΕ ΤΟ ΔΕΡΜΑ: Πλύνετε με άφθονο νερό και σαπούνι. Εάν παρατηρηθεί ερεθισμός του δέρματος ή εμφανιστεί εξάνθημα: Συμβουλευθείτε/Επισκεφθείτεγιατρό. Απορρίψτε τα περιεχόμενα/δοχείο σύμφωνα με τους τοπικούς/εθνικούς/διεθνείς κανονισμούς.

(HR)
Upozorenje
Može izazvati alergijsku reakciju na koži.
Nositi zaštitne rukavice/zaštitnu odjelo/zaštitu za oči/zaštitu za lice. U SLUČAJU DODIRA S KOŽOM: oprati velikom količinom sapuna i vode. U slučaju nadražaja ili osipa na koži: zatražiti savjet/pomoć liječnika. Odložite sadržaje /spremnike u skladu s lokalnim/regionalnim/nacionalni/međunarodnim odredbama.

(HU)
Figyelem
Allergiás bőrreakciót válthat ki.
Védőkesztyű/védőruha/szemvédő/arcvédő használata kötelező. HA BŐRRE KERÜL: Lemosás bő szappanos vízzel. Bőrirritáció vagy kiütések

megjelenése esetén: orvosi ellátást kell kérni. Az edény tartalmát / a tartályt a helyi/regionális/nemzeti/nemzetközi szabályozásoknak megfelelően kell hulladékként elhelyezni.

(IT)

Attenzione
Può provocare una reazione allergica cutanea. Indossare guanti/indumenti protettivi/Proteggere gli occhi/il viso. IN CASO DI CONTATTO CON LA PELLE: lavare abbondantemente con acqua e sapone. In caso di irritazione o eruzione della pelle: consultare un medico. Smaltire il prodotto/recipiente in conformità con le disposizioni locali / regionali / nazionali / internazionali.

(LT)

Atsargiai
Gali sukelti alerginę odos reakciją.
Mūvėti apsaugines pirštines/dėvėti apsauginius drabužius/naudoti akių (veido) apsaugos priemones. PATEKUS ANT ODOS: Nuplauti dideliu kiekiu muilo ir vandens. Jeigu sudirginama oda arba ją išberia: kreiptis į gydytoją. Turinį/talpą išpilti (išmesti) - šalinti pagal vietines / regionines / nacionalines / tarptautines taisykles.

(LV)

Uzmanību / Brīdinājums
Gali sukelti alerginę odos reakciją.
Mūvėti apsaugines pirštines/dėvėti apsauginius drabužius/naudoti akių (veido) apsaugos priemones. PATEKUS ANT ODOS: Nuplauti dideliu kiekiu muilo ir vandens. Jeigu sudirginama oda arba ją išberia: kreiptis į gydytoją. Turinį/talpą išpilti (išmesti) - šalinti pagal vietines / regionines / nacionalines / tarptautines taisykles.

(NL)

Waarschuwing
Kan een allergische huidreactie veroorzaken. Beschermende handschoenen/beschermende kleding/oogbescherming/gelaatsbescherming dragen. BIJ CONTACT MET DE HUID: met veel water en zeep wassen. Bij huidirritatie of uitslag: een arts raadplegen. De inhoud en de verpakking verwerken volgens de plaatselijke/regionale/nationale/internationale voorschriften.

(NO)

Advarsel
Kan forårsake allergiske hudreaksjoner. Bruk vernehansker/verneklær/vernebriller/ansiktsskjerm. VED HUDKONTAKT: Vask med store mengder vann og såpe. Ved hudirritasjon eller -utslett: Kontakt / tilkall lege. Innholdet / emballasjen skal avhendes i henhold til de lokale / regionale / nasjonale / internasjonale forskrifter.

(PL)

Uwaga
Może powodować reakcję alergiczną skóry. Stosować rękawice ochronne/odzież ochronną/ochronę oczu/ochronę twarzy. W PRZYPADKU KONTAKTU ZE SKÓRĄ: Umyć dużą ilością wody z mydłem. W przypadku wystąpienia podrażnienia skóry lub wysypki: Zasięgnąć porady/zgłosić się pod opiekę lekarza. Zawartość / pojemnik usuwać zgodnie z przepisami miejscowymi / regionalnymi / narodowymi / międzynarodowymi.

(PT)

Atenção
Pode provocar uma reacção alérgica cutânea. Usar luvas de protecção/vestuário de protecção/protecção ocular/protecção facial. SE ENTRAR EM CONTACTO COM A PELE: lavar com sabonete e água abundantes. Em caso de irritação ou erupção cutânea: consulte um médico. Eliminar o conteúdo/recipiente de acordo com a legislação local/regional/nacional/internacional.

(RO)

Atenţie
Poate provoca o reacţie alergică a pielii. Purtaţi mănuşi de protecţie/îmbrăcăminte de protecţie/echipament de protecţie a ochilor/chipament de protecţie a feţei. ÎN CAZ DE CONTACT CU PIELEA: spălaţi cu multă apă şi săpun. În caz de iritare a pielii sau de erupţie cutanată: consultaţi medicul. Aruncaţi conţinutul/containerul în acord cu regulamentele locale/regionale/naţionale/internaţionale.

(SE)

Varning
Kan orsaka allergisk hudreaktion.
Använd skyddshandskar/skyddskläder/ögonskydd/ansiktsskydd. VID HUDKONTAKT: Tvätta med mycket tvål och vatten. Vid hudirritation eller utslag: Sök läkarhjälp. Innehållet / behållaren avfallshanteras enligt lokala / regionala / nationella / internationella föreskrifter.

(SI)

Pozor
Lahko povzroči alergijski odziv kože.
Nositi zaščitne rokavice/zaščitno obleko/zaščito za oči/zaščito za obraz. PRI STIKU S KOŽO: umiti z veliko mila in vode. Če nastopi draženje kože ali se pojavi izpuščaj: poiščite zdravniško pomoč/oskrbo. Vsebino/vsebnik odstranite v skladu z lokalnimi/regionalnimi/narodnimi/mednarodnimi predpisi.

(SK)

Pozor
Môže vyvolať alergickú kožnú reakciu.
Noste ochranné rukavice/ochranný odev/ochranné okuliare/ochranu tváre. PRI KONTAKTE S POKOŽKOU: Umyte veľkým množstvom vody a mydla. Ak sa prejaví podráždenie pokožky alebo sa vytvoria vyrážky: vyhľadajte lekársku pomoc/starostlivosť. Zneškodnenie obsahu/obalu v súlade s miestnymi/oblastnými/národnými/medzinárodnými nariadeniami.

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