

EB VCA IgM EIA

ID: White

Enzyme Immunoassay (EIA) for the Detection of EB VCA IgM Antibodies in Human Serum.

For *In Vitro* Diagnostic Use Only

25185 • 96 Tests

FOR REFERENCE USE ONLY

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1 - INTENDED USE

For the qualitative detection of human IgM antibodies to Epstein-Barr (EB) viral capsid antigen (VCA) in human serum by enzyme immunoassay, as an aid in differentiating active or recent Epstein-Barr virus infection from past infection. These reagents have not received FDA clearance for use in testing blood or plasma donors.

2 - SUMMARY AND EXPLANATION OF THE TEST

This summary does not intend to imply additional performance claims other than those already indicated in the Intended Use section.

Epstein-Barr virus (EBV) is the etiological agent of infectious mononucleosis (IM), and has also been implicated in Burkitt's lymphoma and nasopharyngeal carcinoma.¹ The designation of infectious mononucleosis classically refers to an Epstein-Barr virus-induced illness in young adults characterized by reactive blood smears, exudative pharyngitis, prominent cervical lymphadenopathy, and serologically detectable heterophile antibodies. These clinical manifestations can also be caused by a number of other pathogenic agents including cytomegalovirus, *Toxoplasma gondii*, rubella virus, hepatitis virus, human immunodeficiency virus (HIV), and uncommonly by drugs such as Halothane, Hydantoin, Dapasone, and Azulfidine.^{2,3,4}

Diagnosis of acute EBV IM is generally confirmed by a positive heterophile antibody test. The severity of the disease, however, is not indicated by the relative titer of heterophile antibodies.⁵ In addition, difficulties in diagnosis arise when the heterophile antibody test is negative, or when the clinical manifestations are atypical or unusually severe.

Heterophile-negative IM occurs in 10 to 20 percent of adults, and in an even greater percentage of children.^{6,7} IM diagnosis in these individuals may be confirmed by the detection and identification of antibodies to specific EB antigens which include: viral capsid antigen (VCA), early antigens, diffuse and restricted (EA-D and EA-R), and Epstein-Barr nuclear antigen (EBNA).

IgG antibodies to VCA may be present early during EBV infection, but they persist indefinitely after the occurrence of clinical disease and may merely indicate EBV infection at some time in the past. IgM antibodies to VCA, on the other hand, are present in the circulation 1 to 6 weeks after the onset of EBV illness and usually disappear in 3 to 6 months. Thus the presence of VCA IgM usually suffices for the diagnosis of acute

IM. Further verification may be obtained by testing for the presence of antibodies directed against the other EBV-specific antigens, early antigen and EBNA. Heterophile antibody negative sera demonstrating VCA IgM and transient levels of antibody to early antigen are considered diagnostic for acute IM. In contrast, antibodies to EBNA appear late during IM infections, and IgG antibodies to EBNA may persist for years, even for life, and are indicative of the convalescent phase of IM infection.

The EB VCA IgM EIA test is an ELISA test which utilizes a microwell format. Test results are obtained after one and one-half hours incubation time. They are objective and normalized as Index values, permitting uniformity of reporting.

3 - PRINCIPLE OF THE TEST

Diluted samples are incubated in VCA antigen-coated wells. *Absorbents have been included in the Diluent to neutralize the effects of rheumatoid factor and IgG antibody.* VCA IgM antibodies (if present) are immobilized in the wells. Residual sample is eliminated by washing and draining, and conjugate (enzyme labeled antibodies to human IgM) is added and incubated. If IgM antibodies to VCA are present, the conjugate will be immobilized in the wells. Residual conjugate is eliminated by washing and draining, and the substrate is added and incubated. In the presence of the enzyme, the substrate is converted to a yellow end product which is read photometrically.

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4 - REAGENTS

EB VCA IgM EIA Product Description Catalog No. 25185 (96 Tests)

Component	Contents	Preparation
Coated Wells 12 eight-well strips	<ul style="list-style-type: none">Coated with Epstein-Barr virus gp125 antigenWhite wells	Use as supplied. Return unused strips to pouch and reseal. Do not remove desiccant.*
Well support 1 Frame	<ul style="list-style-type: none">Plate frame	Use as supplied.
Diluent** 1 bottle (25 mL)	<ul style="list-style-type: none">Phosphate-buffered saline with a protein stabilizer, and absorbents for rheumatoid factor and IgG antibodyPink Color	Use as supplied.
Calibrator** 1 vial (0.6 mL)	<ul style="list-style-type: none">Human serum; moderately reactive for VCA IgM antibodiesIndex value shown on vial label	Dilute in Diluent as described.
Positive Control** 1 vial (0.6 mL)	<ul style="list-style-type: none">Human serum; reactive for VCA IgM antibodiesIndex values shown on vial label	Dilute in Diluent as described.
Negative Control** 1 vial (0.6 mL)	<ul style="list-style-type: none">Human serum; nonreactive for VCA IgM antibodies	Dilute in Diluent as described.
Conjugate** 2 bottles (12 mL)	<ul style="list-style-type: none">Goat anti-human IgM labeled with alkaline phosphatase (calb)Green Color	Use as supplied.
Substrate*** 1 bottle (12 mL)	<ul style="list-style-type: none">p-Nitrophenyl phosphate	Use as supplied.
Wash Concentrate** 1 bottle (30 mL)	<ul style="list-style-type: none">Tris-buffered salineTween 20™pH 8.0	Dilute in 1 liter of distilled or deionized water.
Stop Reagent 1 bottle (12 mL)	<ul style="list-style-type: none">Trisodium phosphate 0.5 M	Use as supplied.

* The color of the desiccant does not affect the performance of the kit.

** Contains 0.1% sodium azide.

*** The substrate may develop a slight yellow color during storage. One hundred microliters of substrate should yield an absorbance value less than 0.35, when read in a microwell against air or water.

Store these reagents at 2-8°C up to the expiration date indicated on the bottle labels. Do not allow them to contact the skin or eyes. If contact occurs, wash with copious amounts of water. Do not remove desiccant.

5 - OTHER MATERIALS REQUIRED

1. Microplate washer
2. Pipettors for dispensing 8, 100, and 200 µL
3. Timer
4. 1 or 2 liter container for Wash Solution
5. Distilled or deionized water
6. Dilution tubes or microwells
7. Microwell reader capable of reading absorbance at 405 nm

6 - PRECAUTIONS FOR USERS

For *In Vitro* Diagnostic Use



1. Test samples, Calibrator(s), Controls, and the materials that contact them should be handled as potential biohazards. The calibrators and controls have been tested and found to be non-reactive for HIV, hepatitis B surface antigen, and HCV antibodies by licensed tests. However, no method can offer complete assurance that HIV, hepatitis B virus, HCV, or other infectious agents are absent. Handle reagents and patient samples as if capable of transmitting infectious disease following recommended *Universal Precautions* for bloodborne pathogens as defined by OSHA⁹, Biosafety Level 2 guidelines from the current CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories*¹⁰, WHO *Laboratory Biosafety Manual*¹¹, and/or local, regional, and national regulations.
2. The concentrations of anti-EB VCA IgM in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity.
3. Avoid contact with open skin.
4. Never pipet by mouth.
5. Certain test reagents contain dilute **sodium azide**, which may be harmful if enough is ingested (more than supplied in kit). Azides are reported to react with lead and copper in plumbing to form compounds that may detonate on percussion. If disposing of solutions containing sodium azide down drains, flush with large volumes of water to minimize the build-up of metal-azide compounds. Dispose of contents and container in accordance with local, regional, national, and international regulations.
6. For more hazard information, refer to the product Safety Data Sheet (SDS), which is available at www.bio-rad.com and upon request.

- Any lot number of the following reagents may be used with this assay provided they have the correct catalog number and are not used beyond their labeled expiration date:

- Diluent - Catalog # 25188
- Substrate - Catalog # 25192
- Wash Concentrate - Catalog # 25190
- Stop Reagent - Catalog # 25191

Do not mix any other reagents from different lots.

- Do not use reagents beyond their stated expiration date.
- Incubation times recommended in the Test Procedure section should be adhered to.
- Unused Coated Wells should be kept in their resealable bag with desiccant and stored in the refrigerator.
- This product should be used by qualified personnel.
- There are no health hazards associated with the intact desiccant packet. Do not cut, split, or otherwise compromise it as dusts that may be generated could pose a health hazard. If the desiccant has been compromised, do not remove it from the plate pouch.

7 - SPECIMEN COLLECTION, PREPARATION, AND STORAGE

Sera should be separated from clotted blood. If specimens are not tested within 8 hours, they should be stored at 2 to 8°C for up to 48 hours. Beyond 48 hours, specimens should be stored at -20°C or below. More than one freeze-thaw cycle should be avoided. Samples containing visible particulate matter should be clarified by centrifugation; and hemolyzed, icteric, or grossly contaminated samples should not be used. Samples should not be heat-inactivated before testing.

8 - TEST PROCEDURE

Materials Provided

See REAGENTS section on page 5.

EIA Procedure

- Allow all reagents and patient samples to reach room temperature before use. Return them promptly to refrigerator after use.
- Prepare working wash solution by adding entire bottle of Wash Concentrate (30 mL) to 1 liter of water. Once diluted,

the wash solution can be stored at room temperature for up to two months, or at 4°C until the expiration date printed on the Wash Concentrate bottle.

3. Prepare 1:26 dilutions of test samples, Calibrator, Positive and Negative Controls in the test set Diluent. For example: add 8 μL of sample to 200 μL of Diluent in a dilution well or tube and mix well.
4. Place appropriate number of Coated Wells in the Well Support.

Note: For combination testing (multiple assays per plate), the strips should be assembled on a white background with good lighting. Be sure to note the placement of each strip and the corresponding color.

5. Transfer 100 μL of the diluted Calibrator, Control, and patient sample to the wells.

Note: Include one well which contains 100 μL of Diluent only. This will serve as the reagent blank and will ultimately be used to zero the photometer before reading the test results.

6. Incubate the wells at room temperature (20 to 25°C) for 30 \pm 5 minutes.
7. Wash wells four times, with at least 250 μL of wash solution per well. Do not allow the wells to soak between washes. Aspirate thoroughly after the last wash.
8. Place 2 drops (or 100 μL) of Conjugate into each well.
9. Incubate the wells at room temperature (20 to 25°C) for 30 \pm 5 minutes.
10. Wash wells four times with at least 250 μL of wash solution per well. Do not allow the wells to soak between washes. Aspirate thoroughly after the last wash.
11. Place 2 drops (or 100 μL) of Substrate into each well.
12. Incubate at room temperature (20 to 25°C) for 30 \pm 5 minutes.
13. Place 2 drops (or 100 μL) of Stop Reagent into each well. Tap the plate gently, or use other means to assure complete mixing.
14. Read and record the absorbance of the contents of each well at 405 nm against the reagent blank.

Note: Adjust the photometer to zero absorbance at 405 nm against the reagent blank. Readings should be made within 2 hours after the reactions have been stopped.

9 - QUALITY CONTROL

Test Validation Criteria

1. The Calibrator(s), Positive and Negative Controls must be included in each test run.
2. The absorbance value of the Calibrator must be ≥ 0.200 , when read against the reagent blank.
3. The absorbance value of the reagent blank should be < 0.350 .
4. The Negative Control must have an Index value < 0.9 .
5. The Positive Control must have an Index value equal to or greater than 1.1. Users may supply an alternative Positive Control which yields index values close to the assay cutoff, to challenge the assay at its critical level, if they wish.
6. The Negative and Positive Controls have been prepared from different lots of materials than the Calibrator, and are intended to monitor for substantial reagent failure. The Positive Control will not ensure precision at the assay cutoff. Additional controls may be tested according to guidelines or requirements of local, state, and/or federal regulations or accrediting organizations. For guidance on appropriate quality control practices, please refer to NCCLS document C24-A, *Internal Quality Control Testing: Principles and Definitions*.
7. If any of these criteria are not met, the test is invalid and should be repeated. If the test is invalid, patient results can not be reported.

10-INTERPRETATION OF RESULTS

Calculation of Results

Determine the Index value for each test sample (or Control) using the following formula:

$$\frac{\text{Calibrator Index}}{\text{Calibrator Absorbance}} \times \text{Test Sample Absorbance} = \text{Test Sample Index}$$

If the Calibrator is run in duplicate, use the average absorbance value to calculate results.

Interpretation of Results

Index Value	Interpretation
< 0.9	Negative for anti-EB VCA IgM antibody
≥ 0.9 and < 1.1	Equivocal*
≥ 1.1	Positive for anti-EB VCA IgM antibody

* Index values which fall between 0.9 and 1.1 indicate an equivocal result. Subsequent samples should be drawn at least fourteen days later and tested simultaneously with the initial sample. If the subsequent sample is positive, seroconversion has occurred, which may be indicative of recent infection. If the subsequent sample remains equivocal, antibody status is undetermined and the sample is deemed equivocal. Other clinical and serological evidence should be sought in these cases.

Negative results do not rule out the diagnosis of disease associated with Epstein-Barr virus. The specimen may be drawn before appearance of detectable antibodies. Negative results in suspected early disease should be repeated in 3-4 weeks. This information should accompany the reporting of results to the clinician.

The EB VCA IgM EIA cutoff values were based on statistical analyses of the results of tests of 126 serum specimens that were negative for anti-VCA IgM antibodies when tested by another commercial VCA IgM test.

The presence of IgM antibody to EB VCA suggests recent or current infection. Specimens that yield absorbance values above the range of the test set Calibrator may be pre-diluted in the test set Diluent and reassayed. The resulting Index value must be multiplied by the dilution factor. Example: If the specimen has been pre-diluted 1:5 before testing, the resulting Index value should be multiplied by 5.

Values obtained with different manufacturers' assay methods may not be used interchangeably. The magnitude of the reported IgM level cannot be correlated to an endpoint titer. The magnitude of the assay result above the cutoff is not an indicator of the total antibody present.

11-LIMITATIONS

The results obtained with the EB VCA IgM EIA test serve only as an aid to diagnosis and should not be interpreted as diagnostic in themselves. Test results should be evaluated in relation to patient symptoms, clinical history, and other laboratory findings.

The timing of the appearance of IgM antibodies to VCA is subject to variations among individuals and serological assays.

Anti-VCA specific IgG may compete with IgM for binding sites, leading to false negative results. Rheumatoid factor, in the presence of specific IgG, may contribute to false positive results. The absorbent in the EB VCA IgM EIA Diluent is intended to

neutralize the effects of rheumatoid factor and specific IgG. Studies have indicated that the absorbent was able to neutralize up to 98% of the activity in a sample known to contain 3,328 IU/mL of rheumatoid factor activity.

Some sera drawn very early at the onset of symptoms may not contain detectable levels of VCA IgM antibody and may require the drawing of another test specimen 1-2 weeks later.

The prevalence of the analyte will affect the assay's predicative value.

Testing should not be performed as a screening procedure on the general population. The predicative value of a positive or negative serologic result depends on the pretest likelihood of Epstein-Barr associated disease being present. Testing should only be done when clinical evidence suggests the diagnosis of this syndrome.

This assay is not intended for viral isolation and/or identification.

The assay's performance characteristics have not been established for matrices other than serum.

The assay's performance characteristics have not been established for testing newborn specimens or cord blood.

Performance has not been adequately established in a pediatric population.

Performance characteristics have not been established for immunosuppressed individuals.

The assay's performance characteristics have not been established for visual result determination.

12-EXPECTED VALUES

Nearly all individuals have been infected with EBV by the time they reach adulthood.⁸ Characteristically, IgG antibodies to VCA appear relatively early during IM infections and persist for years, even for life.

IgM antibodies to VCA rise during the acute phase of EBV infection, and decline to undetectable levels between the first week and twelfth week after onset of symptoms. According to a large epidemiological study, the highest incidence of symptomatic IM occurs in adolescents, 15-24 years, and varies due to seasonal, ethnic, and geographical factors.

Serum samples obtained randomly from fifty normal South Florida blood donors were assayed by the EB VCA IgM EIA test.

Forty-nine samples (98%) were negative for IgM antibodies to VCA. One sample was equivocal, having an Index value of 0.9. This sample was negative when tested by another microwell ELISA method. The mean Index value obtained for the fifty normal donors was 0.1.

13-PERFORMANCE CHARACTERISTICS

Comparative Testing

The results of EB VCA IgM EIA tests correlate well with other commercial serological tests. Serum specimens obtained from normal South Florida blood donors, from patients whose sera were submitted to a South Florida clinical laboratory for EBV serology, and from serum brokers, were assayed by the EB VCA IgM EIA test and other commercial serological assays. The assays were performed at an independent laboratory (Lab A, Miami, FL) and at Laboratory B (Miami, FL). Thirty (34.1%) of the serum specimens tested at Laboratory A were from female donors, ranging in age from 1 to 54 years (mean = 25 years). Thirty-four (38.6%) were from male donors ranging in age from less than 1 year to 91 years (mean = 35 years). Twenty-four (27.3%) of the donors were not identified. The test population included 16 specimens (18%) obtained from infants, adolescents, and young adults ranging in age from 1 month to 29 years, which were evenly divided between males and females. All of the specimens in the clinical studies were frozen prior to testing. The results obtained in these studies are shown below in Tables 1 and 2, respectively.

Table 1: Results of tests of 88 archival patient specimens tested at an independent clinical laboratory (Laboratory A) Miami, FL, using the EB VCA IgM EIA test and another commercial IFA test.

Comparative Test #1	EB VCA IgM EIA			
	Positive	Negative	Equivocal	Total
Positive	29	0	2	31
Negative	3	54	0	57
Equivocal	0	0	0	0
Total	32	54	2	88

Overall agreement $[(TP + TN) / (TP + TN + FP + FN)] = 96.5^*$

95% CI = 90.1 to 99.3**

* Excluding equivocal results

** Calculated by the exact method

Table 2: Results of tests of 157 archival patient specimens tested at Laboratory B (Miami, FL) using the EB VCA IgM EIA test and another commercial EIA test.

Comparative Test #2	EB VCA IgM EIA			
	Positive	Negative	Equivocal	Total
Positive	26	5	0	31
Negative	3	121	2	126
Equivocal	0	0	0	0
Total	29	126	2	157

Overall agreement $[(TP + TN) / (TP + TN + FP + FN)] = 94.8\%$ *

95% CI = 94.8 to 98.3% **

* Excluding equivocal results

** Calculated by the exact method

Sensitivity and specificity relative to serological profile

One hundred and fifty-seven archival serum specimens (see Table 2) were tested at Laboratory B using the EB VCA IgM EIA test and other commercially available EIA tests for detecting VCA IgG, VCA IgM, and EBNA IgG antibodies. One hundred and thirty-nine of these sera were able to be characterized as acute (VCA IgM antibody present and EBNA IgG antibody absent), seropositive (VCA IgG and EBNA IgG antibodies present and VCA IgM antibodies absent), or seronegative (no serological evidence of EBV IgM, EBV IgG, or EBNA IgG antibodies) on the basis of their serological profile. The sensitivity, specificity, and agreement of the EB VCA IgM EIA assay were determined based on these characterizations. It was assumed that the VCA IgM response should be negative for the seronegative samples and the samples from past infections, and positive for the acute samples. The results have been summarized below in Table 3.

Table 3: Results of tests performed at Laboratory B with 139 pre-selected serum specimens, using the EB VCA IgM EIA test and other commercially available tests for VCA IgG, VCA IgM, and EBNA IgG antibodies.

EB VCA IgM EIA	Serum Characterization		
	Acute VCA IgM Positive EBNA IgG Negative	Past Infection VCA IgM Negative VCA IgG Positive EBNA IgG Positive	Seronegative VCA IgM Negative VCA IgG Negative EBNA IgG Negative
Positive	26	3	0
Negative	1	96	10
Equivocal	0	3	0
Total	27	102	10

	Samples*	%	95 % C.I.**
Relative sensitivity (Acute)	26/27	96.3	81.1% to 99.9
Relative sensitivity (Past Infection)	96/99	97.0	91.4% to 99.4
Relative specificity (Seronegative)	10/10	100	69.2% to 100
Relative agreement	132/136	97.1	92.2% to 99.9

* Equivocal results were not included in the calculations, nor were they retested

** 95% confidence intervals (CI) were calculated using the exact method

Cross-reactivity

The EB VCA IgM EIA test does not cross-react with antibodies directed against the other herpes viruses: cytomegalovirus, varicella-zoster virus, and herpes simplex virus. Thirteen serum specimens that were shown to be negative when assayed with the EB VCA IgM EIA test were shown to be positive for IgM antibodies directed against the other herpes viruses including: 4 containing herpes simplex virus IgM antibody, 4 with cytomegalovirus IgM antibody, and 5 with varicella-zoster virus IgM antibody. The herpes IgM and CMV IgM antibodies were detected with IgM-specific enzyme immunoassays, and the varicella-zoster IgM antibodies were detected by fluorescent antibody membrane antigen (FAMA) assay. The level of antibodies in these serum specimens was 1.4 to 6.3 times the assay cutoff value of herpes simplex virus IgM assay, 1.7 to 2.2 times the cutoff of the cytomegalovirus assay, and 2 to 4 times the cutoff of the varicella-zoster virus assay. These results, shown below in Table 4, indicate that the EB VCA IgM EIA test does not cross-react with IgM antibodies directed against the other herpes viruses.

Table 4: Results of EB VCA IgM EIA assays of 13 serum specimens shown to be positive for IgM antibodies directed against other herpes viruses.

Sample ID	VCA-M Index* $\sqrt{\sqrt{}}$	CMV-M Index* $\sqrt{\sqrt{}}$	HSV-M Index* $\sqrt{\sqrt{}}$	VZV-M Index* $\sqrt{\sqrt{}}$
Q002-27-150C	0.7, Neg	2.2	ND	ND
Q002-27-150D	0.9, Neg	2.0	ND	ND
Q002-27-150E	0.5, Neg	1.9	ND	ND
Q002-27-150F	0.6, Neg	1.7	ND	ND
Q002-27-170C	0.4, Neg	ND	4.3	ND
Q002-27-170D	0.6, Neg	ND	3.6	ND
Q002-27-170E	0.7, Neg	ND	4.2	ND
Q002-27-170F	0.1, Neg	ND	1.6	ND
Q021-3-1	0.3, Neg	ND	ND	2.0
Q021-3-2	0.5, Neg	ND	ND	4.0
Q021-3-3	0.4, Neg	ND	ND	2.0
Q021-3-4	0.7, Neg	ND	ND	4.0
Q021-3-5	1.0, Equ	ND	ND	4.0

* Index value = Observed value divided by assay cutoff value

$\sqrt{\sqrt{}}$ Index value ≥ 1.1 = Positive

$\sqrt{\sqrt{}}$ Index value ≥ 1.0 = Positive

ND - Not done

IgM Specificity Study

Five serum specimens which contained EB VCA-specific IgM and EB VCA-specific IgG were assayed by the EB VCA IgM EIA and EB VCA IgG EIA tests, before and after treatment with 2-mercaptoethanol. This treatment denatures IgM but does not affect IgG antibodies. The results of this experiment are shown in Table 5, below.

Table 5: Results obtained for EB VCA IgM EIA and EB VCA IgG EIA assays of 5 serum specimens containing EB VCA-specific IgG and IgM, before and after treatment with 2-mercaptoethanol.

Sample	VCA IgM Index		VCA IgG Index	
	Before	After	Before	After
1	1.5	0	8.8	9.0
2	2.0	0	1.8	2.3
3	2.2	0	1.7	1.2
4	5.4	1.5	15.1	19.1
5	8.0	0	4.1	3.4

After treatment with 2-mercaptoethanol, the EB VCA IgM antibodies in all five specimens were neutralized, while the EB VCA IgG antibodies were not significantly affected. These results demonstrate that the EB VCA IgM EIA test is specific for detecting EB VCA IgM antibodies.

Precision

Six serum specimens (5 positives and 1 negative) and the EB VCA IgM EIA Positive and Negative Controls were assayed in triplicate on three separate occasions. These results are shown below in Table 6.

Table 6: Results intra-assay and inter-assay precision tests performed at Laboratory B. Values were calculated from EB VCA IgM EIA index values.

SAMPLE	INTRA-ASSAY			INTER-ASSAY		
	MEAN INDEX	S.D	C.V. %	MEAN INDEX	S.D	C.V. %
Pos. Control	2.2	0.306	14.1	2.1	0.265	12.8
Neg. Control	0.6	0.058	NA	0.5	0.000	NA
1	0.2	0.000	NA	0.2	0.073	NA
2	7.7	0.635	8.3	7.6	0.604	8.0
3	2.7	0.100	3.7	2.7	0.101	3.8
4	3.6	0.379	10.6	3.6	0.273	7.6
5	2.4	0.208	8.6	2.3	0.220	9.5
6	3.0	0.058	1.9	2.8	0.194	6.8

14-REFERENCES

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