Commercial serologic assays for varicella-zoster virus (VZV), which enable reliable determination of VZV immune status and are amenable to automation, are needed. The present study compares the automated performance of the VZV whole-cell enzyme-linked immunosorbent assay (ELISA) Enzygnost anti-VZV/IgG, the Euroimmun anti-VZV ELISA (IgG) based on highly purified viral proteins, and the VZV glycoprotein (gp)-based Serion ELISA Classic VZV IgG. The fluorescent-antibody-to-membrane-antibody (FAMA) test was used as a reference. A total of 638 serum samples from VZV-negative children, blood donors, varicella vaccinees, and bone marrow transplant recipients were included. The Enzygnost anti-VZV/IgG and the Serion ELISA Classic VZV IgG showed sensitivities of 99.6% and 99.2%, respectively, and the Euroimmun anti-VZV ELISA (IgG) had a significantly lower sensitivity of 90.5%. Specificity was calculated as 100% for both the Euroimmun anti-VZV ELISA (IgG) and for the Enzygnost anti-VZV/IgG, and the Serion ELISA Classic VZV IgG had a significantly lower specificity of 89.4%. Quantitative results of all ELISAs correlated well, but there was a poor quantitative correlation between the ELISAs and FAMA. In conclusion, this study does not show any superiority of a gp- and a protein-based ELISA compared to a whole-cell ELISA for the automated detection of VZV-specific IgG. The automated performance of the Enzygnost anti-VZV/IgG assay correlated best with the FAMA reference assay.

Varicella-zoster virus (VZV) is one of the most common pathogens that affects humans. The primary infection leads to typical signs of varicella, also termed chicken pox. Thereafter, the virus can remain latent lifelong in trigeminal and dorsal root ganglia. Endogenous viral reactivation, thought to be associated with waning VZV-specific T-cell-mediated immunity (8), leads to herpetic episodes, especially in older adults and immunocompromised persons. Seroepidemiological studies revealed that the prevalence of VZV-specific IgG class antibodies shows a rapid increase during the first decade of life and reaches more than 90% in developed countries (5, 17, 26). Varicella is usually perceived as a mild and self-limiting disease during childhood. The incidence of reported complications is low (6), but their frequency and severity increase with age (1). In addition, varicella is a special risk for immunocompromised patients (7), and pregnant women are at risk of life-threatening maternal pneumonia or congenital diseases of the newborn (21). Thus, several countries have implemented routine childhood vaccination. Studies indicate that this intervention strategy may provide economic benefits for both the individual and the society (3).

In individuals who are at risk of serious varicella or its complications, it is important to clarify the susceptibility to varicella and the protection against subsequent infection, both of which correlate with the presence of IgG class antibodies to VZV in serum (11, 16). Furthermore, with the widespread use of varicella vaccine, response to immunization has to be assessed in special groups of persons, such as health care workers and immunocompromised patients (19). There is agreement that the fluorescent-antibody-to-membrane-antigen (FAMA) test, which detects VZV glycoprotein (gp)-specific antibodies, correlates best with susceptibility to and protection against clinical varicella (9). However, FAMA is labor-intensive, time-consuming, and not amenable to automation, and the inherent subjectivity of interpretation of results requires extensive experience (4, 18). All these disadvantages confine its use to virological laboratories that are highly specialized in the field of VZV diagnostics and research. Therefore, commercial enzyme-linked immunosorbent assays (ELISAs) are widely used for the determination of antibody status to VZV in routine diagnostics. Most of these assays rely on lysate from whole cells infected with VZV for specific antigen, and only a few use purified VZV gp. Although individual commercial VZV gp ELISAs have been validated in comparison to VZV whole-cell ELISAs (20, 22), the use of both types of ELISAs is controversial and gp ELISAs have not been accepted broadly.

The objective of this study was to compare the VZV whole-cell ELISA Enzygnost anti-VZV/IgG test distributed by Siemens Healthcare Diagnostics (Marburg, Germany), the VZV protein-based ELISA Euroimmun anti-VZV ELISA (IgG) from Euroimmun (Lübeck, Germany), and the VZV gp-based Serion ELISA Classic VZV IgG test distributed by Virion/Serion (Würzburg, Germany). To this end, 638 serum samples from VZV-negative children, blood donors, varicella vaccinees, and bone marrow
transplant recipients were used. Furthermore, 146 problem serum samples preselected in the routine diagnostics step using the Enzygnost anti-VZV/IgG were included in this study.

MATERIALS AND METHODS

**Serum panels.** To compare the performance of three VZV IgG ELISAs, a total of 638 sera were included. A total of 109 sera were from VZV-seronegative infants and children aged 5 months to 3 years (panel 1), among whom 68 were male and 41 female. A total of 420 sera were obtained from blood donors 19 to 65 years old (panel 2). A total of 216 sera were from men, and 204 were from women. For each age, between 4 and 10 male and female individuals were included. In addition, a group of 57 sera was obtained from varicella vaccinees 1 to 38 years old (panel 3). Fifteen vaccinees were male, 19 were female, and the gender was not known for 23. These persons had been immunized with one or two doses of the varicella vaccines Varilrix (GlaxoSmithKline, Uxbridge, United Kingdom) or Varivax (Aventis Pasteur MSD SpA, Rome, Italy) ≥ 4 to 6 weeks before the sera were taken. Finally, there were 52 sera from 21 patients, 12 men and 9 women, between 7 months and 22 years of age, after bone marrow transplantation (panel 4). From each patient, between 2 and 4 serum samples were obtained sequentially, in order to show the frequency of seroconversion and/or seroreversion of VZV-specific IgG using FAMA (i.e., when a VZV IgG-negative result was followed by a VZV IgG-positive result, or vice versa). The characteristics of all 4 serum panels are summarized in Table 1.

Furthermore, 146 sera received from the Institute of Medical Virology, Charité University Hospital (Berlin, Germany) were tested (Table 1). These sera were preselected by routine screening with the Enzygnost assay over a period of 2 years. The only characteristic of these sera was that they contained ≥ 50 mIU/ml, corresponding to a cutoff value of 0.1 ΔA (difference in absorbance between viral antigen and control antigen), which were interpreted as negative.

TABLE 1 Characteristics of serum panels

| Serum panel | Characteristics of sera                                                                 | No. of serum samples obtained | Sampling period |
|-------------|----------------------------------------------------------------------------------------|------------------------------|-----------------|
| P1          | VZV-seronegative children, tested by FAMA, 5 mos to 3 yrs old                        | 109                          | 1997–2006       |
| P2          | Blood donors 19–65 yrs old, 4–10 males or females/age                                | 420                          | 1997–2006       |
| P3          | Varicella vaccinees, 2–35 yrs old; sera obtained ≥ 4 to 6 wks after one or two doses of Varilrix or Varivax recipients 5–14 yrs old | 57                           | 2004–2011       |
| P4          | Sequential serum samples (2–4/patient) showing seroconversion, from 21 bone marrow transplant | 52                           | 2003–2008       |
| Total for P1–P4 |                                                                                      | 638                          |                 |
| P5          | Sera from routine diagnostic tests that were VZV IgG negative by Enzygnost anti-VZV/IgG (Siemens) | 73                           | 2009–2010       |
| P6          | Sera from routine diagnostic tests that were VZV IgG borderline by Enzygnost anti-VZV/IgG (Siemens) | 73                           | 2009–2010       |
| Total for P5 and P6 |                                                                                      | 146                          |                 |

**Test Manufacturer VZV-specific antigens Calibration (reference) Cutoff value**

| Test                      | Manufacturer     | VZV-specific antigens                      | British standard for VZV antibodies (19) | First international standard for varicella immunoglobulin (13) | 1:2 | 50 mIU/ml |
|---------------------------|------------------|-------------------------------------------|------------------------------------------|---------------------------------------------------------------|-----|----------|
| FAMA                     | Siemens Healthcare Diagnostics | VZV glycoproteins Extract from whole cells infected with VZV strain Ellen; control antigen(s) extracted from noninfected cells | First international standard for varicella immunoglobulin (13) | First international standard for varicella immunoglobulin (13) | 1:2 | 50 mIU/ml |
| Enzygnost anti-VZV/IgG ELISA |                   |                                           |                                           |                                                               |     |          |
| Serion ELISA Classic VZV IgG | Virion/Serion   | VZV envelope gp                           |                                           |                                                               |     |          |
| Anti-VZV-ELISA (IgG)     | Euroimmun        | Highly purified VZV proteins of strain Ellen |                                           |                                                               |     |          |
microtitration wells (20). VZV antibody levels are expressed in mIU/ml and are assessed according to the Serion standard curve method. The specification of antibody activity was in reference to the WHO standard specified in the First International Standard for Varicella Zoster Immunoglobulin (13) was declared as 50 IU per vial. Following the recommendation of the RKI (15), results equivalent to 110 mIU/ml anti-VZV IgG were interpreted as positive, 50 to 110 mIU/ml as equivocal, and <50 mIU/ml as negative.

The Euroimmun anti-VZV ELISA (IgG) from Euroimmun (Lübeck, Germany) was the third VZV ELISA tested (catalog number EI 2650-9601 G; lots E110513AK and E110718AL). According to the information provided by the manufacturer, this ELISA uses highly purified VZV proteins of the VZV reference strain Ellen as antigen, which is bound to the surface of microtitration wells. Quantification was realized by evaluating standard curves based on 4 kit-specific calibrators. In contrast to the recommendation of the RKI (15), positive results were equivalent to 110 mIU/ml anti-VZV IgG, equivocal results were between 80 and 110 mIU/ml, and results of <80 mIU/ml were interpreted as negative. The controls of the ELISA have been calibrated with the international anti-varicella-zoster serum W1044 (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands). After the test plates were prepared with the dispensed samples according to the manufacturer’s protocol, all ELISAs were performed automatically using the BEP III system (Siemens Healthcare Diagnostics) and following the IFUs. Assay definitions for the non-Siemens assays on the BEP III system have been established by strictly following the assay procedure according to the IFUs and based on the kit-specific controls and standard sera/calibrators as well as a panel of representative sera covering the measuring range. All validation criteria according to the IFUs were fully met. Aspects of test robustness and reproducibility were addressed by using a panel of familiarization samples with graded reactivities.

### Statistical analyses.
For all ELISAs, equivocal results after retesting were considered reactive and, therefore, added to the positive results. This decision was made prior to the start of this study and was in line with the Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (23). Sensitivity was calculated as the proportion of positive sera

| Test assay and FAMA result | No. positive by test assay in panel: | No. negative by test assay in panel: | Sensitivity (%) | Specificity (%) | Correlation (%) |
|---------------------------|------------------------------------|-----------------------------------|----------------|---------------|----------------|
FIG 1 Comparison of quantitative results obtained by FAMA with those of the Enzygnost anti-VZV/IgG, Serion ELISA Classic VZV IgG, and Euroimmun anti-VZV ELISA (IgG) tests with 419 positive sera from the blood donors of panel 2. Each dot is the results of a single sample.
RESULTS
The results for serum panels 1 to 4 are summarized in the Table 3. Both the Enzygnost anti-VZV/IgG and the Euroimmun anti-VZV ELISA (IgG) tests had 100% specificity, while the Serion ELISA Classic VZV IgG had a significantly lower specificity, 89.4% (P < 0.0001). The sensitivities of the Enzygnost anti-VZV/IgG and Serion ELISA Classic VZV IgG assays were 99.6% and 99.2%, respectively. In comparison, the Euroimmun anti-VZV ELISA (IgG) test had a significantly lower sensitivity, 90.5% (P < 0.0001). There was a 99.7% correlation between the results of the Enzygnost anti-VZV/IgG and FAMA tests, while the correlation between the Serion ELISA Classic VZV IgG results and the FAMA test were significantly lower, at 97.0% (P = 0.0002). The Euroimmun anti-VZV ELISA (IgG) correlated with the FAMA result for 92.6% of all samples tested. This correlation differed significantly from the correlations of the Enzygnost anti-VZV/IgG (P < 0.0001) and Serion ELISA Classic VZV IgG tests (P < 0.0005) with the FAMA test.

Based on the results of serum panels 5 and 6 (Table 4), sensitivities of 89.3% for the Serion ELISA Classic VZV IgG and 83.9% for the Enzygnost anti-VZV/IgG were determined, and there was a significantly lower sensitivity of 3.6% for the Euroimmun anti-VZV ELISA (IgG) (P < 0.0001). The specificity was calculated as 100% for the Euroimmun anti-VZV ELISA (IgG), 86.7% for the Enzygnost anti-VZV/IgG test, and 75.6% for the Serion ELISA Classic VZV IgG test. All these differences were significant (P < 0.0003). The correlations with FAMA were 85.6% for the Enzygnost anti-VZV/IgG, 80.8% for the Serion ELISA Classic VZV IgG, and significantly lower, at 63.0%, for the Euroimmun anti-VZV ELISA (IgG) (P ≤ 0.001).

As shown in Fig. 1, the comparison of quantitative results obtained by FAMA with the results of the Enzygnost anti-VZV/IgG, Serion ELISA Classic VZV IgG, and Euroimmun anti-VZV ELISA (IgG) tests for the positive sera from blood donors of panel 2 revealed that FAMA titers did not show a narrow correlation with the concentrations of VZV IgG, given in mIU/ml, independent of the ELISA used. Each FAMA titer between 1:2 and 1:32 referred to low and high VZV IgG concentrations measured by the different ELISAs, even though a tendency for higher VZV IgG concentrations in all ELISAs was evident with higher FAMA titers. The comparison of quantitative results obtained with the Enzygnost anti-VZV/IgG, Serion ELISA Classic VZV IgG, and Euroimmun anti-VZV ELISA (IgG) tests shown in Fig. 2 revealed that VZV IgG concentrations measured by the Enzygnost anti-VZV/IgG and Serion ELISA Classic VZV IgG tests had a good correlation, while the Euroimmun anti-VZV ELISA (IgG) resulted in considerably higher values, above 1,000 mIU/ml. The Pearson correlation coefficient ranged between 0.855 for the correlation between the Enzygnost anti-VZV/IgG and Serion ELISA Classic VZV IgG tests and 0.869 for the correlation between the Enzygnost anti-VZV/IgG and Euroimmun anti-VZV ELISA (IgG) tests.

DISCUSSION
The present study is one of the most comprehensive head-to-head comparisons of three commercial ELISAs for the determination of immune status to VZV. The tests were chosen because (i) they are CE-marked assays used widely in Europe, especially in Germany, (ii) they are based on different viral antigens, and (iii) they are performed and evaluated fully automatically after pipetting of samples and controls. The first ELISA is based on VZV whole-cell antigen (Siemens), the second on highly purified VZV proteins (Euroimmun), and the third uses VZV gp (Virion/Serion), for which the potential advantage is the strong correlation of gp-specific antibodies with protection against varicella (9, 24, 25). The ELISA using purified viral proteins might show improved specificity by reduction of interference from cellular antigens. However, single viral antigens may produce test sensitivities inferior to those with preparations containing many different antigens, while whole-cell ELISAs have the full composition of viral antigens but might also detect antacellular antibodies. The results for the basic study population revealed high sensitivities of 99.6% for the VZV whole-cell ELISA Enzygnost anti-VZV/IgG test from Siemens and 99.2% for the VZV gp-specific Serion ELISA Classic VZV IgG test distributed by Virion/Serion. However, while the Siemens ELISA Enzygnost anti-VZV/IgG test showed an excellent specificity of 100%, the specificity of the Serion ELISA Classic VZV IgG test was reduced significantly, to 89.4%. The main reason for this was that a considerable number of FAMA-negative sera from infants and bone marrow transplant recipients reacted positively. The Euroimmun anti-VZV ELISA (IgG) test had an excellent specificity, 100%, but the sensitivity was clearly diminished, to 90.5%. In this ELISA, the number of positives was obviously reduced in the serum panels from blood donors, varicella vaccinees, and bone marrow transplant recipients. A possible reason for these differences might be a concentration of VZV gp in the antigen used for the Euroimmun anti-VZV ELISA (IgG) that is too low. It has to be considered that for the calculation of sensitivities described above, equivocal results were interpreted as positive. However, when equivocal results were excluded from this calculation, the sensitivities of the Enzygnost anti-VZV/IgG (99.6%), Serion ELISA Classic VZV IgG (99.2%), and Euroimmun anti-VZV ELISA (IgG) (90.4%) tests were not changed or changed only marginally.

The high sensitivity of the gp-based Serion ELISA Classic VZV IgG confirmed findings of a previous study, but in the previous study only 180 sera were included, and the performance of the test was not automated or standardized (20). Surprisingly, the specificity of this ELISA was reduced to 89% here, compared to 100%
specificity in the earlier (2006) study. These findings can only be interpreted in the context of the approximately 3-fold-higher number of FAMA-negative sera included in the current study. In fact, the whole-cell ELISA Enzygnost anti-VZV/IgG showed a comparable high sensitivity accompanied by 100% specificity in relation to FAMA. Thus, the performance of the VZV ELISA currently distributed by Siemens is better than in studies published previously (12, 20). Maple et al. (12) reported a reduced specificity of 80.7% associated with an excellent sensitivity. However, it is likely that those authors used a panel of negative sera that was too small for a realistic determination of the specificity. In addition, by their use of a relatively high cutoff value (93.3 mIU/ml) in the reference assay (a time-resolved fluorescence immunoassay), nearly all equivocal (reactive) sera in the Enzygnost anti-VZV/IgG were evaluated as negative by the reference method.

Due to the fact that diagnostic samples from a mainly adult population show only a low percentage of negative and borderline results for VZV IgG and to better address the aspects of specificity and detection limits, this study also included problem sera from routine diagnostic testing. These sera were preselected using the Enzygnost anti-VZV/IgG test and were samples that resulted in negative or equivocal results and, therefore, were excluded from the calculations of overall sensitivity and specificity. However, our findings also show that the Enzygnost anti-VZV/IgG and the Serion ELISA Classic VZV IgG have the best balance between sensitivity and specificity in this critical panel, ranging between 76 and 89%. The Enzygnost anti-VZV/IgG test showed slightly different results for three preselected Enzygnost-negative sera of panel 5 (conversion from negative to equivocal) and in 17 preselected sera of panel 6 (reversion from equivocal to negative), in comparison to the results with routine diagnostics (Tables 1 and 4).

One should, however, be aware that these different test results are most likely caused by the borderline nature of these samples. As the typical intra- and interassay coefficients of variation demonstrated (data not shown), the test results of one sample may vary between negative and equivocal or between equivocal and positive. The equivocal range of the Enzygnost anti-VZV/IgG assay ranges from 0.1 to 0.2 AU, and transitions of such equivocal samples to negativity or positivity are not unusual.

In contrast to natural VZV immunity, the determination of postvaccine immunity to VZV has to be considered a significantly stronger measure for VZV IgG ELISAs. The reason for this is that the VZV antibody response after immunization with live-attenuated VZV vaccine has been reported to be >10-fold lower than after natural infection (9, 14). In Germany, routine varicella vaccination has been recommended since 2004, but sera from vaccinees are hard to obtain, since there is no routine serological screening of postvaccine immunity. Therefore, only 57 sera taken ≥4 to 6 weeks after immunization with one or two doses of a varicella vaccine could be included in this study. Similar to the overall results, the Enzygnost anti-VZV/IgG (96%) and the Serion ELISA Classic VZV IgG (92%) showed the best sensitivities for the determination of antibody response after varicella vaccination, whereas the Euroimmun anti-VZV ELISA (IgG) (45%) had a poor sensitivity for the detection of seroconversion after vaccination.

As the positive findings in the group of blood donors demonstrated, all ELISAs had a good correlation of quantitative results, and the Euroimmun anti-VZV ELISA (IgG) resulted in considerably more values above 1,000 mIU/ml, despite a reduced sensitivity. In comparison, this study is the first to demonstrate that a whole-cell ELISA and a gp ELISA for the determination of VZV IgG did not show a real correlation of quantitative results with FAMA. This suggests that the Serion ELISA Classic VZV IgG may not be based only on VZV gp but also partially on lysate from whole cells infected with VZV. This might be a possible reason for the reduced specificity. As described by Krah et al. (10), an ELISA with highly purified VZV gp in the solid phase results in relatively low titers that reach a plateau. These data correspond to the results with FAMA obtained in this study.

In summary, the present study does not show any superiority of a gp- and a protein-based ELISA compared to a whole-cell ELISA for the automated detection of VZV-specific IgG. Whereas both the VZV gp-specific Serion ELISA Classic VZV IgG distributed by Virion/Serion and the whole-cell ELISA Enzygnost anti-VZV/IgG from Siemens had high sensitivities approaching 100%, the specificity of the Serion ELISA Classic VZV IgG was considerably reduced. The protein-based Euroimmun anti-VZV ELISA (IgG) had an excellent specificity, but the sensitivity was reduced significantly.

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