Medicinal Research Reviews

WILEY

REVIEW ARTICLE

Advances in Nanotechnology-Enabled Optical Biosensors for Dengue Virus Detection: A Systematic Review

Marta Quero-Delgado[1] | Helena Codina[1] | Rafael Gómez[2,3,4,5] | Francisco José Terán[6,7] | M. A. Muñoz-Fernández[3,8,9] | José Luis Jiménez[9,10] | Salvador Resino[1,11] | Daniel Sepúlveda-Crespo[1,11] | Isidoro Martínez[1,11]

[1]Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología, Instituto de Salud Carlos III (Campus Majadahonda), Majadahonda, Madrid, Spain | [2]Departamento de Química Orgánica y Química Inorgánica, Universidad de Alcalá, Alcalá de Henares, Madrid, Spain | [3]Networking Research Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Madrid, Spain | [4]Instituto de Investigación Química "Andrés M. del Río", Universidad de Alcalá, Alcalá de Henares, Madrid, Spain | [5]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain | [6]iMdea Nanociencia, Ciudad Universitaria de Cantoblanco, Madrid, Spain | [7]Nanobiotecnología (iMdea-Nanociencia), Unidad Asociada al Centro Nacional de Biotecnología (CSIC), Madrid, Spain | [8]Section of Immunology, Immuno-Molecular Biology Laboratory (LIBM), University General Hospital Gregorio Marañon (HGUGM), Madrid, Spain | [9]Gregorio Marañon Health Research Institute (IiSGM), Madrid, Spain | [10]Laboratory Platform, University General Hospital Gregorio Marañon (HGUGM), Madrid, Spain | [11]Centro de Investigación Biomédica en Red en Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

Correspondence: Daniel Sepúlveda-Crespo (danisecre@hotmail.com; daniel.sepulveda@isciii.es) | Isidoro Martínez (imago@isciii.es)

Received: 1 October 2024 | **Revised:** 17 June 2025 | **Accepted:** 14 July 2025

Funding: This study was supported by grants from Instituto de Salud Carlos III (ISCII; grant #PI23CIII/00018 to D.S.-C. and I.M., PI19CIII/00009 to I.M., PI20CIII/00004 to S.R., PI23/01137, PT23/00148 to M.A.M.F.). This study was also supported by the Consorcio Centro de Investigación Biomédica en Red (CIBER) (CB 2021), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea—NextGenerationEU: CIBERINFEC (CB21/13/00044 to S.R.) and CIBER-BBN (CB22/01/00041 to M.A.M.F.). D.S.-C. is a "Miguel Servet" researcher from ISCIII (grant #CP23CIII/00004). Programa de Investigación de la Consejería de Sanidad de la Comunidad de Madrid to J.L.J.

Keywords: dengue virus | diagnostics | nanomaterials | optical biosensor | point-of-care

ABSTRACT

The dramatic surge in dengue cases in early 2024, endangering half the global population, urgently necessitates faster diagnostic methods. Nanotechnology-enabled optical biosensors offer a promising avenue, leveraging nanomaterial properties for highly sensitive detection of dengue virus (DENV), potentially surpassing conventional techniques in terms of simplicity, speed, and cost-effectiveness. This systematic review analyzes recent advancements in these biosensors for DENV diagnosis. Following PRISMA 2020 guidelines, we systematically searched PubMed, Embase, Scopus, Web of Science, and Cochrane Library databases (2010–June 1, 2025; OSF: https://osf.io/3gmey/). The methodological quality of the 98 included studies was assessed using a modified CASP checklist. Diverse nanotechnology-based optical biosensors were identified. SPR (36.7%) was the most

Abbreviations: Ag, silver; AI, artificial intelligence; AgNP, silver nanoparticle; AI&ML, artificial intelligence and machine learning; AlN, aluminum nitride; aM, attomolar; ASSURED, affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free, and deliverable to end-users; Au, gold; AuNP, gold nanoparticle; $BaTiO_3$, barium titanate; BRET, bioluminescence resonance energy transfer; C, dengue virus capsid protein; CASP, critical appraisal skills program; cDNA, complementary DNA; CdS, cadmium sulfide; CdSeS, cadmium selenide sulfide; CdSeTe, cadmium selenide telluride; CdZnSeS, cadmium zinc selenium sulfide; CRISPR, clustered regularly interspaced short palindromic repeat; DENV, dengue virus; DHF, dengue hemorrhagic fever; DNA, deoxyribonucleic acid; DSS, dengue shock syndrome; E, dengue virus envelope protein; ELISA, enzyme-linked immunosorbent assay; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; Y-Fe_2O_3, maghemite nanoparticle; Fe_3O_4, magnetite nanoparticle; FLISA, fluorescence-linked immunosorbent assay; FRET, Förster resonance energy transfer; GOx, graphene oxide; ICC, intraclass correlation coefficient; IgG, immunoglobulin G; IgM, immunoglobulin M; IoMT, Internet of Medical Things; κ, Cohen's Kappa coefficient; LoD, limit of detection; M, dengue virus membrane protein; MesH, Medical Subject Headings; ML, machine learning; NH_2, amine; NP, nanoparticle; NS, nonstructuraldengue virus protein; OSF, Open Science Framework; PAMAM, polyamidoamine; PICO, problem, intervention, comparison, outcome; PNA, peptide nucleic acid; PoC, poin-of-care; PRISMA, preferred reporting items for systematic review and meta-analysis; QD, quantum dot; rGOx, reduced graphene oxide; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; scFV, single-chain fragment variable antibody; SERS, surface-enhanced Raman scattering; SPR, surface plasmon resonance; ssDNA, single-stranded DNA; $TiSi_2$, titanium disilicide; TOF, tapered optical fiber; WNV, West Nile virus; WS_2, tungsten disulfide; YFV, yellow fever virus; ZIKV, Zika virus; zM, zeptomolar; ZnO, zinc oxide; ZnS, zinc sulfide.

Marta Quero-Delgado and Helena Codina contributed equally to this study.

Senior authors Salvador Resino, Daniel Sepúlveda-Crespo, and Isidoro Martínez contributed equally to this study.

common transducer, followed by fluorescence (24.5%), colorimetry (15.3%), and SERS (8.2%). Gold-based nanomaterials (35.7%) were most frequently employed, with silver nanomaterials (15.3%), quantum dots (15.3%), and graphene-based materials (15.3%) also showing promise. DENV NS1 protein was the primary target analyte (21.4%). Importantly, almost half of the studies (44.9%) used clinically relevant human samples. While many optical biosensors show promise, challenges hinder their demonstration of the true potential for point-of-care use in their current format; however, they offer high specificity and faster results, laying a strong foundation for cost-effective clinical diagnostics. Nanotechnology-driven optical biosensors offer a transformative approach for DENV detection. Advances in computational design and green synthesis of novel nanomaterials are key to addressing stability and field-deployment challenges. These innovations are crucial for developing robust, sensitive, and user-friendly tools to manage dengue and improve patient outcomes globally.

1 | Introduction

1.1 | Dengue Virus: Biology, Epidemiology, and Global Impact

Dengue virus (DENV), a member of the *Flaviviridae* family [1], is a positive-stranded ribonucleic acid (RNA) virus responsible for a significant global health burden [1, 2]. The viral genome, approximately 11 Kb in length [1, 3], encodes three structural proteins (membrane [M], envelope [E], and capsid [C]) and seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) [3]. All these proteins are crucial for the viral lifecycle, including replication, assembly, and immune evasion [4, 5]. The E protein, in particular, is vital for viral entry and serves as a key target for neutralizing antibodies [6]. Differences in its sequence define the four main DENV serotypes (DENV1–4) [7], with a fifth (DENV5) also proposed [8]. Understanding these viral components is fundamental for developing targeted diagnostic and therapeutic strategies.

Primarily transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes [2, 3], DENV causes an estimated 100 to 400 million infections annually across tropical and subtropical regions [1, 2]. The geographical reach of DENV has expanded alarmingly in recent decades, with over 10 million cases reported worldwide in early 2024 and increasing occurrences in previously nonendemic areas, including parts of Europe [1, 2]. Currently, about half of the world's population is at risk, and by June 2024, DENV had resulted in over 5000 deaths across 80 countries [1, 2]. The high prevalence of asymptomatic or mild infections further complicates epidemiological surveillance and outbreak control, underscoring the urgent need for sensitive and readily deployable diagnostic tools [1]. The expanding global impact and the complexities of DENV transmission underscore the critical role of accurate and timely diagnosis in mitigating disease spread and severity.

1.2 | Clinical Aspects of Dengue and the Need for Early Diagnosis

The clinical presentation of DENV infection is remarkably diverse, ranging from asymptomatic cases or mild, nonspecific febrile illness to severe, life-threatening conditions such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [2, 9]. DHF is characterized by plasma leakage, which can disrupt homeostasis and progress to DSS, a condition involving shock, bleeding, and potential organ failure [1, 10]. While some symptoms are common across serotypes, serotype-specific manifestations have also been reported [3]. The distinction between a primary DENV infection (first exposure) and a secondary infection (infection with a different serotype following a previous one) is clinically significant, as DHF and DSS are mainly associated with secondary infections [11–13]. The complexity of its clinical manifestations, often mimicking other febrile illnesses, poses a diagnostic challenge, particularly in the early stages of the disease [14].

Compounding this diagnostic challenge is the lack of specific antiviral therapies for DENV infection. Current patient management is primarily supportive, aimed at relieving symptoms such as pain and carefully managing complications, including plasma leakage, especially in severe cases [1, 15–17]. While analgesics are commonly used, nonsteroidal anti-inflammatory drugs are generally avoided due to the increased risk of bleeding [18]. Although some antiviral candidates are under investigation and limited vaccines, such as Dengvaxia and Qdesnga, have been approved with specific indications and restrictions [3, 10, 15–17, 19, 20], widely effective and universally applicable therapeutic or broadly deployed preventive measures remain elusive. This critical therapeutic and preventive gap underscores the paramount importance of early and accurate diagnosis. Early detection is essential not only for appropriate clinical management and patient triage (interventions that can reduce mortality in severe dengue) but also for implementing effective public health surveillance and outbreak control measures. Therefore, the development and deployment of advanced diagnostic tools that offer rapid, sensitive, and specific detection are pivotal in addressing the global dengue burden.

1.3 | Advances in Dengue Diagnosis: From Traditional Methods to Nanotechnology-Enabled Optical Biosensors

Diagnosing DENV infection traditionally relies on a combination of direct methods, which detect the virus or its components (e.g., virus isolation, NS1 antigen detection, viral RNA amplification), and indirect methods, which identify the host's immune response (e.g., immunoglobulin M [IgM] and immunoglobulin G [IgG] antibodies) [10, 12, 21] (see Supplemental File 1: Table S1). While direct methods offer accuracy in early infection, and indirect methods are useful later in the disease course, conventional assays present several limitations. These

include potential false positives due to antibody cross-reactivity with other flaviviruses, especially in regions with low DENV prevalence [12]; the need for differential diagnosis from other febrile illnesses, such as Chikungunya or Zika [22]; and often, a requirement for specialized laboratory infrastructure and skilled personnel [23]. The high prevalence of DENV in tropical and developing countries, coupled with these limitations, has spurred the demand for simple, inexpensive, and rapid point-of-care (PoC) diagnostic tests, driving the development of new technologies to replace or augment traditional assays [23].

In this context, biosensors have emerged as a promising alternative. A biosensor integrates biological recognition elements with a transducer to detect an analyte and generate a measurable signal (Figure 1A) [21]. This review focuses on optical biosensors, which quantify analyte concentration by detecting changes in light properties such as absorption, reflection, or emission [24, 25]. These can be label-free, directly converting the analyte-bioreceptor interaction into a signal, or label-based, requiring tags to generate a detectable signal (Figure 1B) [26, 27]. Common optical transduction techniques for DENV detection include fluorescence, luminescence, colorimetry, surface plasmon resonance (SPR), and surface-enhanced Raman scattering (SERS) [24, 28, 29].

The performance of optical biosensors has been significantly enhanced by nanotechnology. This field enables the precise engineering of materials at the nanoscale, offering unique properties that have found diverse applications in biomedicine [30–34], including advanced imaging [35], sophisticated drug delivery and targeted therapies [36–42], and tissue engineering [43]. Crucially for diagnostics, nanotechnology provides powerful tools for biosensing and biomarker detection [44–51]. Nanomaterials such as nanoparticles (NPs), quantum dots (QDs), nanorods, or nanowires can amplify signals, improve limits of detection (LoDs), and increase specificity by enhancing optical properties and providing large surface areas for bioreceptor immobilization [21, 52–54]. Compared to traditional methods, nanotechnology-enabled optical biosensors often provide faster analysis, lower power consumption, and higher sensitivity, making them highly suitable for PoC applications in DENV diagnostics. While detailed nanomaterial design is beyond the scope of this review (see [55–62] for comprehensive details), their integration is pivotal for advancing DENV detection.

The field of DENV detection has been the subject of numerous reviews, covering a wide spectrum, from conventional diagnostic tools to emerging biosensor technologies [63–65]. More recent critical reviews have broadly summarized advancements in DENV-based biosensors [66, 67], and general overviews of dengue have been systematically reviewed [68]. However, the rapid advancements in nanotechnology and optical detection modalities necessitate a focused and methodologically rigorous synthesis of evidence. To our knowledge, no systematic review has been specifically dedicated to nanotechnology-enabled optical biosensors for DENV detection. Such a review is crucial not only to consolidate the current state-of-the-art in this specific niche but also to critically evaluate the quality of the existing evidence, identify research gaps, and discuss translational barriers and prospects, thereby providing a distinct and valuable contribution to the existing body of literature.

1.4 | Objective

This systematic review highlights recent advancements in nanotechnology-enabled optical biosensors for diagnosing DENV from 2010 to the present (June 1, 2025).

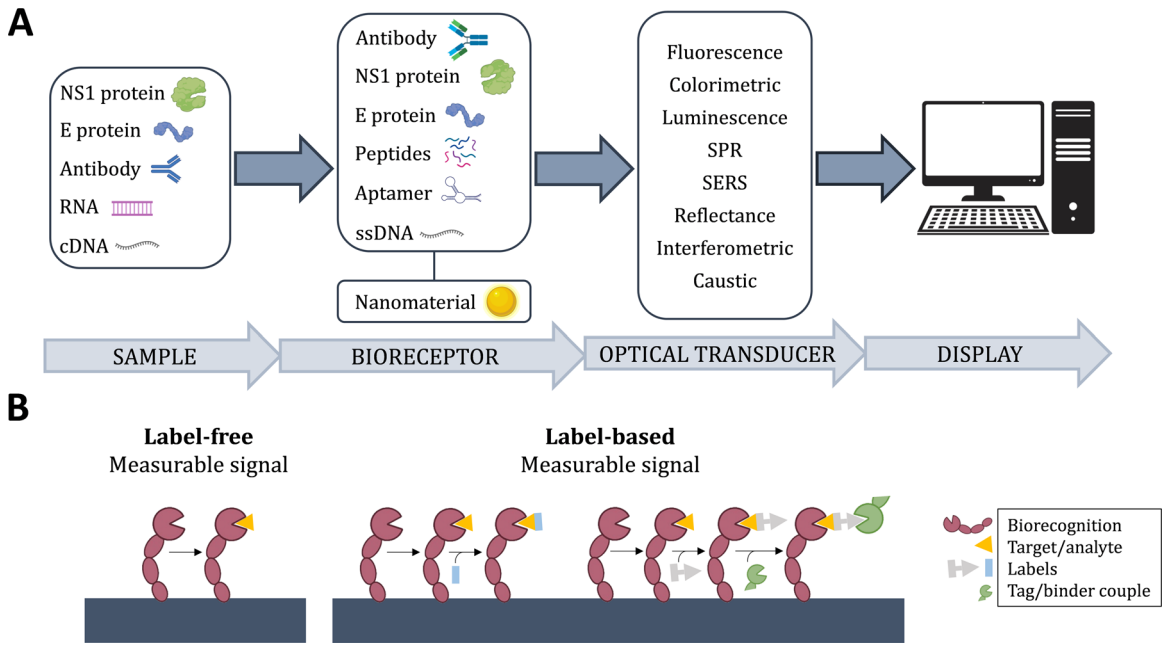

FIGURE 1 | Optical biosensor components and detection methods. (A) Schematic representation of a typical optical biosensor highlighting its key elements: (i) the target/analyte (the substance of interest); (ii) the bioreceptor (recognizes the analyte); (iii) the transducer (converts recognition into a signal); and (iv) the signal processing unit (amplifies and converts signals). (B) Illustration depicting the two main recognition approaches used in optical biosensors: label-free and label-based detection. [Color figure can be viewed at wileyonlinelibrary.com]

2 | Methodology

2.1 | Protocol and Registration

This systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement guidelines [69] to promote transparency and reproducibility (see Supplemental File 2). The study protocol was preregistered in the Open Science Framework [70, 71] (OSF; https://osf.io/3gmey/), and related materials are available in the OSF repository (DOI: 10.17605/OSF.IO/45QKW).

2.2 | Search Strategy

A comprehensive literature search was conducted to identify all relevant articles published from 2010 to June 1, 2025. We searched several electronic databases, including Medline/PubMed, Embase, Scopus, Web of Science, and the Cochrane Library. The search strategy employed Boolean operators (AND, OR) to combine terms related to (i) DENV (e.g., "dengue," "DENV," "flavivirus"), (ii) diagnosis and detection (e.g., "diagnosis," "detection," "PoC"), (iii) biosensing devices and methods (e.g., "biosensor," "optical sensor," "immunoassay," "SPR," "fluorescence," "SERS," "colorimetric"), and (iv) nanotechnology elements (e.g., "nanomaterial," "nanoparticle," "quantum dot," "graphene"). No restrictions on language or geographic location were applied. The reference lists of included studies were also manually searched for additional articles. Full, detailed search strings for each database, demonstrating the specific keywords and their combinations, are provided in Supplemental File 3. All search results and cited references were managed using EndNote X9 (Clarivate Analytics) and exported to Microsoft Excel 2016 spreadsheets (Microsoft Corporation) for further processing.

2.3 | Eligibility Criteria

The research questions were formulated following the problem, intervention, comparison, outcome (PICO) framework [72]. These questions were: What nanotechnology-based biosensors are used with optical detection systems for DENV detection? What optical detection methods have been investigated for DENV using nanotechnology-based biosensors? Which of these methods offers the lowest LoD, defined as the smallest amount of a substance that can be reliably detected? What types of samples can be analyzed by these biosensors? Studies were selected for this systematic review based on the following predefined eligibility criteria.

2.3.1 | For Inclusion

- Original research articles published from 2010 to June 1, 2025.
- Studies describing the development, characterization, or application of biosensors utilizing optical detection systems specifically designed for the detection of DENV or its components (e.g., whole virus, NS1 protein, E protein, viral RNA, anti-DENV antibodies).
- Studies where the biosensor incorporated any nanomaterial, nanostructure, or a closely related element derived from nanotechnology (e.g., NPs, QDs, nanorods, graphene).
- Studies reporting quantitative experimental data on biosensor performance, such as LoD, sensitivity, specificity, or analysis time, or detailing the sample types analyzed (e.g., human clinical samples, spiked samples, cell culture supernatants).
- Studies published in any language or from any geographic location.

2.3.2 | For Exclusion

- Nonoriginal research, including review articles, meta-analyses, systematic reviews, study protocols, case reports, editorials, letters to the editor, author responses, comments, and book chapters.
- Nonpeer-reviewed publications such as preprints or conference abstracts without sufficient data for a full assessment.
- Studies for which only abstracts were available or where full-text articles could not be retrieved.
- Studies with duplicate or substantially overlapping data with previously included publications.
- Studies where essential data for the review (e.g., on the nanomaterial used, the optical detection principle, or performance metrics) could not be reliably extracted.
- Studies describing biosensors that did not employ an optical transduction mechanism.
- Studies that exclusively evaluated commercially available DENV diagnostic kits without novel modification, development, or independent research application.

2.4 | Study Selection and Data Extraction

Two reviewers (MQ-D, HC) independently removed duplicate records and screened the titles and abstracts of all retrieved articles against the pre-defined eligibility criteria. The full-text articles of potentially relevant studies were then obtained and independently assessed by the same two reviewers for final inclusion. Any disagreements at either the title/abstract screening stage or the full-text review stage were resolved through discussion between the two reviewers. If a consensus could not be reached, a third reviewer (DS-C) was consulted to arbitrate and make the final decision. The reasons for excluding studies at the full-text screening stage were documented (e.g., use of nonoptical detection methods or absence of nanomaterials). The study selection process is depicted in a PRISMA flow diagram (Figure 2A). Inter-reviewer agreement for the study selection process was assessed using Cohen's Kappa coefficient (κ). The level of agreement was interpreted according to Landis and Koch's benchmarks: κ values of 0–0.20 indicate slight agreement; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and > 0.80, almost perfect agreement [73].

Data from the eligible studies were independently extracted by two reviewers (MQ-D, HC) using a standardized data extraction form

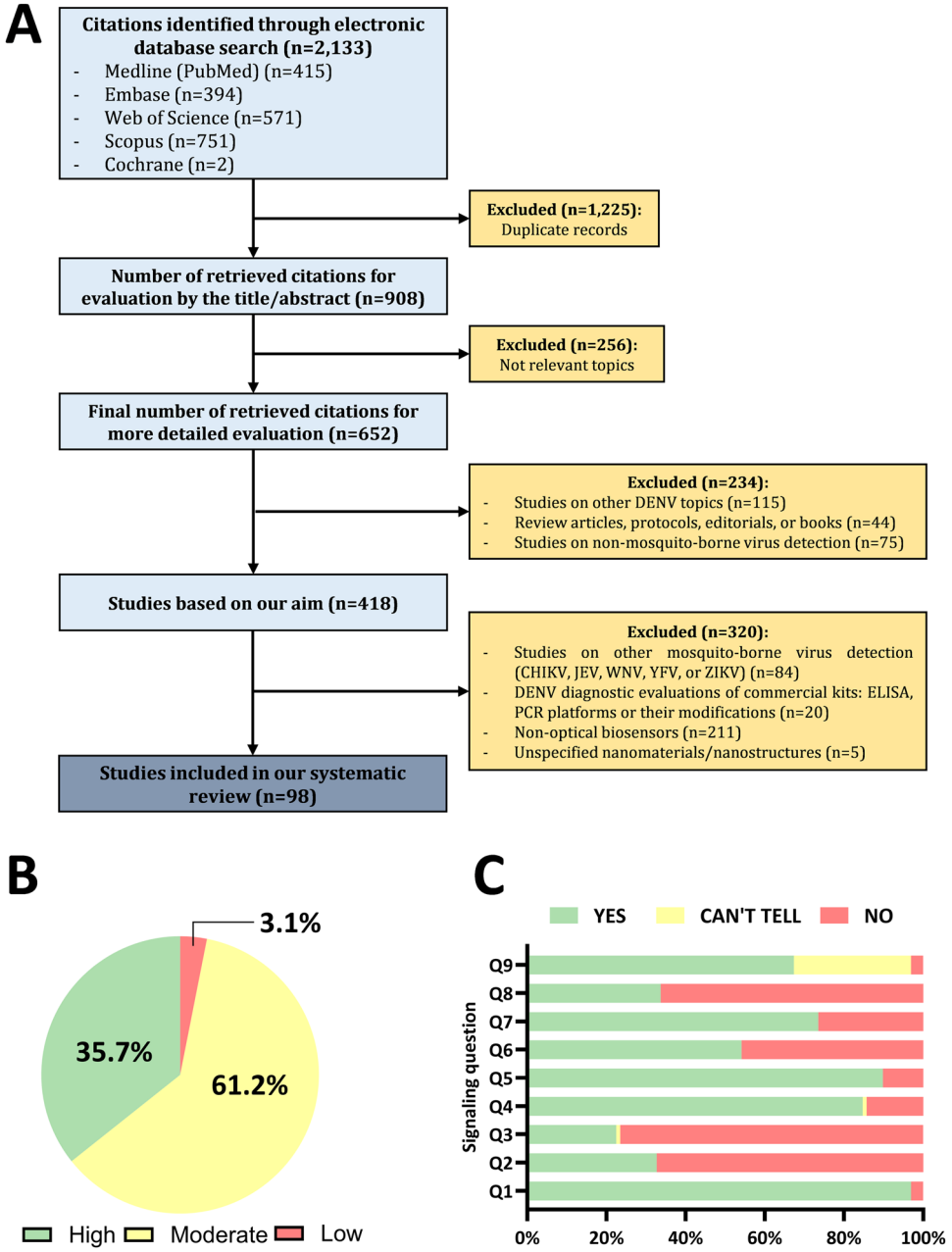

FIGURE 2 | Study selection and quality assessment. (A) Flowchart of the study search process. (B, C) Quality assessment of eligible studies according to a modified CASP checklist for diagnostic test studies. Panel B shows the percentage of high, moderate, or low-quality eligible studies. Panel C presents the percentage of eligible articles with "yes," "no," or "can't tell" responses to each of the nine questions (Q1–Q9). CASP, critical appraisal skills program; CHIKV, Chikungunya virus; DENV, dengue virus; ELISA, enzyme-linked immunosorbent assay; JEV, Japanese encephalitis virus; PCR, polymerase chain reaction; WNV, West Nile virus; YFV, yellow fever virus; ZIKV, Zika virus. [Color figure can be viewed at wileyonlinelibrary.com]

developed for this review. The extracted data included detailed information on (i) the optical transduction mechanism (e.g., SPR, fluorescence, SERS, colorimetry); (ii) the target analyte (e.g., DENV NS1 antigen, DENV E protein, viral RNA, anti-DENV antibodies); (iii) the specific nanomaterial employed (e.g., NPs, QDs, graphene, dendrimers); (iv) DENV serotype specificity and differentiation capability; (v) cross-reactivity with other closely related flaviviruses; (vi) sample type(s) analyzed (including whether they were clinical, spiked, or cell culture-derived); (vii) key evaluation parameters (sensitivity, specificity, LoD with units, analysis time); (viii) PoC potential or suitability; and (ix) any other relevant observations or limitations noted by the study authors. The completeness and accuracy of the extracted data were then thoroughly verified by a third reviewer (DS-C) to ensure consistency and minimize errors.

2.5 | Study Quality Assessment

Methodological quality was assessed using a modified version of the Critical Appraisal Skills Program (CASP) Checklist for diagnostic test studies [54, 74]. We removed five questions deemed

irrelevant to our review's objectives and added two new ones [56] to better align with these objectives. The resulting nine-question checklist was divided into three sections: validity, results, and utility. Studies were rated with "yes" (positive response), "no" (negative response), or "can't tell" (insufficient information) for each question. Three originally qualitative CASP questions were adapted to this format. The scoring system awarded two points for a "yes" response, one point for "can't tell," and zero points for "no," with a maximum score of 18. Studies were categorized as low quality (0–6 points), moderate quality (7–12 points), or high quality (13–18 points) based on previously reported scoring systems [75, 76]. Detailed questions and a summary table of CASP ratings are provided in Supplemental File 4. The methodological quality assessment was conducted independently by two reviewers (MQ-D, HC). Discrepancies between reviewers could arise, such as a lack of clarity in the original study's reporting (where some data might be implicit or incomplete), disagreement about the relevance of the diagnostic test (particularly regarding its applicability or usefulness in clinical practice), or inadvertently overlooking of relevant information. All such discrepancies in scoring or interpretation were thoroughly discussed until a consensus was reached. If a consensus could not be achieved through discussion, a third reviewer (DS-C) was consulted to arbitrate and make the final decision. To quantify the inter-reviewer reliability for the quality assessment scores, the intraclass correlation coefficient (ICC) was calculated. Specifically, a two-way random-effects model, assessing absolute agreement for single rater/measurement, was employed, using IBM SPSS Statistics for Windows, v25 (IBM Corp, Armonk, NY, USA). ICC values were interpreted as follows: <0.5 indicates poor reliability; 0.5–0.75, moderate reliability; 0.75–0.90, good reliability; and >0.90, excellent reliability, based on established guidelines [77, 78].

3 | Study Identification and Characteristics of Included Articles

3.1 | Study Identification and Selection Process

We initially identified 2133 potentially relevant studies. Subsequently, 1715 studies were excluded due to duplication, irrelevant topics, nondetection of DENV, or their status as nonoriginal research, leaving 418 studies. Next, we excluded 320 studies that focused on non-DENV mosquito-borne detection, studies evaluating commercial DENV kits or their modifications, and those not using optical biosensors or lacking precise nanomaterial/nanostructure details. This strict selection yielded a final set of 98 studies aligned with our research focus (Figure 2A). There was substantial agreement between the two reviewers during the title/abstract screening stage ($\kappa = 0.72$) and almost perfect agreement during the full-text eligibility assessment ($\kappa = 0.86$).

3.2 | Overview of Article Characteristics

Our analysis revealed similarities and differences among the optical biosensors developed for DENV detection. They employed various optical detection systems (Tables 1–4). SPR was the most common transducer type ($n = 36$; 36.7%), followed by fluorescence ($n = 24$; 24.5%), colorimetry ($n = 15$; 15.3%), and SERS ($n = 8$; 8.2%). Gold NPs (AuNPs) and Au-derived nanolayers and nanostripes ($n = 35$; 35.7%) were the most frequently used nanomaterials, followed by silver (Ag) nanostructures ($n = 15$; 15.3%), and both QDs and graphene in its various forms ($n = 14$ each; 14.3%). The DENV NS1 protein emerged as the primary target ($n = 21$; 21.4%), followed by the DENV E protein ($n = 15$; 15.3%), anti-DENV antibodies ($n = 14$; 14.3%), and DENV RNA ($n = 8$; 8.2%). The remaining targets included the DENV C protein, complementary deoxyribonucleic acid (cDNA), single-stranded DNA (ssDNA), or undefined DENV antigens. Notably, 10 of the 16 studies targeting the DENV E protein originated from two laboratories.

Regarding sample types, 30 studies (30.6%) used DENV-infected human samples, 14 (14.3%) used spiked human samples, 24 (24.5%) used nonhuman samples, 20 (22.4%) were based on theoretical/computational models and 10 (10.2%) used cell culture supernatants. Concerning serotype specificity, 20 studies (20.4%) developed biosensors capable of detecting all DENV serotypes. More than half of the studies targeted a specific serotype without clarifying multi-serotype applicability ($n = 39$; 39.8%), or did not specify the targeted DENV serotype 39 (39.8%).

4 | Nanotechnology-Powered Optical Biosensors

4.1 | SPR-Based Biosensors

SPR is a sensitive, label-free optical technique used for real-time monitoring of biomolecular interactions via refractive index changes at a metal-dielectric interface [177, 178]. Nanotechnology enhances SPR performance by: (i) amplifying refractive index changes through localized SPR effects or by increasing the mass of bound analytes with high-refractive-index tags; (ii) providing an increased and engineered surface area for optimized bioreceptor immobilization; and (iii) enabling novel signal transduction pathways [52]. Key advancements are summarized in Table 1.

4.1.1 | Gold and Silver Nanostructures

Nanostructures of Au and Ag are central to SPR due to their strong localized SPR effects (collective electron oscillations sensitive to local refractive index changes) and well-defined surface chemistries (e.g., thiol-Au bonds) for robust bioreceptor conjugation [179, 180].

Mechanism and properties: The geometry (e.g., nanospheres, nanorods, layers) and material (Au vs. Ag) of these nanostructures dictate the localized SPR characteristics [79–89]. Analyte binding in the localized SPR-enhanced electromagnetic field near these nanostructures causes a larger shift in the SPR signal compared to planar films. The ease of functionalizing Au with thiolated antibodies or aptamers ensures stable bioreceptor attachment. Nanostructuring increases the surface area, allowing for a higher bioreceptor density, which can improve the probability of analyte capture and the magnitude of the refractive index change. Ag offers stronger plasmonic effects [79], but its susceptibility to oxidation can compromise sensor stability and the integrity of the

TABLE 1 | Key studies on SPR-based optical biosensors for detecting DENV.

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
Gahlaut	2022	Ag nanolayer	DENV NS1	DENV	60 ng/mL	0.2–2 μg/mL	25 min	Human serum samples	Yes	[79]
Loureiro	2017	Au nanolayer	DENV	DENV2–3	2×10^4 particles/mL	NA	30 min	Human serum samples	Yes[b]	[80]
Jahanshahi	2014	Au nanolayer	Anti-DENV IgM Ab	DENV1–4	83/100%[c]	NA	10 min	Human serum samples	Yes	[81]
Kumbhat	2010	Au nanolayer	Anti-DENV IgM Ab	DENV	NA	NA	NA	Human serum/plasma samples	No	[82]
Omar	2018	Au nanolayer–NCC–SPION	DENV E	DENV2	39.96 deg/nM[c]	0.0001–10 nM	NA	E recombinant protein	No	[83]
Wong	2014	Au nanostripe	Anti-DENV IgM Ab	DENV2	NA	NA	NA	Human plasma samples	No	[84]
Basso	2018	AuNP	DENV E	DENV1–4	10^7 $TCID_{50}$/mL	0–200 dilutions	5 min	Cell culture media	No	[85]
Camara[d]	2013	AuNP	DENV NS1	DENV	74 ng/mL	0.05–1 μg/mL	60 min	NS1 recombinant protein	No	[86]
Versiani	2020	AuNR	Anti-DENV E Ab	DENV1–4, ZIKV, YFV, SLEV	1 pg	1 fg–100 pg	30 min	Human serum samples	Yes[b]	[87]
Farooq	2022	AuNS	DENV NS1	DENV	70 ng/mL	NA	> 60 min	NS1 recombinant protein	No	[88]
Mahmood	2021	AuNS	DENV NS1	DENV	70 ng/mL	NA	> 60 min	NS1 recombinant protein	No	[89]
Zhang	2022	GOx–Au nanolayer	Anti-DENV E Ab	DENV	62.5 ng/mL	0.0625–2 μg/mL	120 min	Human serum samples	No	[90]
Omar	2020	rGOx–PAMAM–AuNP	DENV E	DENV2	0.08 pM	0.08–0.5 pM	8 min	E recombinant protein	No	[91]
do Couto	2024	QD	DENV	DENV1-2	NA	0.05×10^{-6}–2×10^{-6} PFU/mL	NA	Human serum samples	No	[92]
Chowdhury	2019	QD-AuNP	DENV RNA	DENV1-4	11.4 fM	1 fM–1 nM	NA	Cell culture media	Yes[b]	[93]
Omar	2019	QD-rGOx–Au nanolayer	DENV E	DENV	0.1 pM	0.1–100 pM	20 min	E recombinant protein	No	[94]

(Continues)

TABLE 1 | (Continued)

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
Omar	2019	QD-GOx–Au nanolayer	DENV E	DENV2	1 pM	0.0001–10 nM	NA	E recombinant protein	No	[95]
Omar	2020	QD-PAMAM–Au nanolayer	DENV E	DENV2	1 pM	0.1–1000 pM	NA	E recombinant protein	No	[96]
Omar	2018	QD-PAMAM–Au nanolayer	DENV E	DENV2	0.1 pM	0.0001–10 nM	NA	E recombinant protein	No	[97]
Yesudasu	2024	Ag–AlN–BP(GO)	DENV	DENV	149.3 deg/RIU[c]	NA	NA	Computational modeling	No	[98]
Karki	2023	Ag–$BaTiO_3$–CeO_2	DENV	DENV	203.2 deg/RIU[c]	NA	NA	Computational modeling	No	[99]
Saini	2025	Ag–BP–CeO_2	DENV	DENV	155.4 deg/RIU[c]	NA	NA	Computational modeling	No	[100]
Daher	2024	Ag–Ni–TiO_2–BP	DENV	DENV	299.4 deg/RIU[c]	NA	NA	Computational modeling	No	[101]
Jena	2025	Ag–TiO_2–AlN–GO	DENV	DENV	182.9 deg/RIU[c]	NA	NA	Computational modeling	No	[102]
Rafi	2025	Ag–TiO_2–WSe_2	DENV	DENV	288.1 deg/RIU[c]	NA	NA	Computational modeling	No	[103]
Basak	2023	Au–$BaTiO_3$–WSe_2	DENV	DENV	128.6 deg/RIU[c]	NA	NA	Computational modeling	No	[104]
Banerjee	2025	Au/ZnS nanogratings	DENV	DENV	14285 nm/RIU[c]	NA	NA	Computational modeling	No	[105]
Machado	2022	AuNR	DENV	DENV, ZIKV, YFV, SLEV	NA	NA	NA	Computational modeling	No	[106]
Senapati	2025	Cu–AlN–$BaTiO_3$	DENV	DENV	430.0 deg/RIU[c]	NA	NA	Computational modeling	No	[107]
Kumar	2024	Cu–BP	DENV	DENV	150.6 deg/RIU[c]	NA	NA	Computational modeling	No	[108]
Kumar	2024	Cu–GaSe–WS_2	DENV	DENV	303.3 deg/RIU[c]	NA	NA	Computational modeling	No	[109]
Uwais	2025	Cu–GO–ITO	DENV	DENV	295.4 deg/RIU[c]	NA	NA	Computational modeling	No	[110]

(Continues)

TABLE 1 | (Continued)

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
Singh	2024	Cu–Si_3N_4–$BaTiO_3$–BP	DENV	DENV	146.5 deg/RIU[c]	NA	NA	Computational modeling	No	[111]
Panda	2022	GO–Sb_2S_3	DENV	DENV	180.8 deg/RIU[c]	NA	NA	Computational modeling	No	[112]
Upender	2025	MXene–GO	DENV	DENV	0.4 THz/RIU[c]	NA	NA	Computational modeling	No	[113]
Almawgani	2023	$TiSi_2$–BP	DENV	DENV	257.3 deg/RIU[c]	NA	NA	Computational modeling	No	[114]

Abbreviations: Ab, antibody; AlN, aluminum nitride; AuNP, gold nanoparticle; AuNR, gold nanorod; AuNS, gold nanosphere; $BaTiO_3$, barium titanate; BP, black phosphorous; CeO_2, cerium oxide; Deg, resonance angle; DENV, dengue virus; DNA, deoxyribonucleic acid; E, envelope protein; GaSe, gallium selenide; GO, graphene; GOx, graphene oxide; IgM, immunoglobulin M; ITO, indium tin oxide; LoD, limit of detection; Mxene, Titanium carbide with surface terminations ($Ti_3C_2T_x$); NA, not available; NCC, nanocellulose; NS1, nonstructural protein 1; PAMAM, polyamidoamine; PFU, plaque forming units; QD, quantum dot; rGOx, reduced graphene oxide; RIU, refractive index unit; SAM, self-assembled molecular; Sb_2S_3, antimony trisulfide; Si_3N_4, silicon nitride; SLEV, Saint Louis encephalitis virus; SPION, superparamagnetic iron oxide nanoparticles; SPR, surface plasmon resonance; $TCID_{50}$, 50% tissue culture infectious dose; THz, terahertz; TiO_2, titanium dioxide; $TiSi_2$, titanium disilicide; WS_2, tungsten disulfide; WSe_2, tungsten diselenide; YFV, yellow fever virus; ZIKV, zika virus.

[a]For an optical biosensor to be considered a PoC device, it should be affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free, and deliverable to end-users, aligning with the ASSURED criteria set by the WHO.

[b]The optical biosensor is designed as a PoC device, although its immediate implementation in certain settings may be limited without prior preparation.

[c]Sensitivity/specificity values.

[d]The analyte detection method is based on localized SPR, although reflectometry is used to read results.

bioreceptor interface [181]. Hybridization of Au films with superparamagnetic iron oxide NPs like magnetite (Fe_3O_4) and nanocellulose aims to optimize these surface interactions for enhanced binding or reduced nonspecific adsorption [83].

DENV antigen detection (NS1, E protein): Direct detection of DENV NS1 in human serum using Ag-nanolayers has yielded clinically relevant LoDs (~60 ng/mL, 25 min) [79]. AuNP-based systems report similar LoDs (~70–74 ng/mL) for recombinant NS1 [86, 88, 89], though often requiring further optimization for complex matrices or ultra-early detection where antigen concentrations are minimal. Rapid detection of DENV E protein (<5 min) has been shown, but at high viral concentrations in cell culture supernatants [85], suggesting that in this setup, faster detection may come at the cost of lower sensitivity. Sensitivity is dependent on antibody affinity, surface orientation and density, and the antigen's size and nature. Nanostructured surfaces can enhance antibody density and proper orientation, improving binding efficiency and signal strength. On the other hand, larger antigens like NS1 (a hexamer in its secreted form) [182] or intact virions can induce a greater refractive index change upon binding compared to smaller peptide epitopes from the E protein.

Host antibody detection: Serological SPR assays benefit from the higher concentration and avidity of antibodies in patient samples (especially IgM, a pentamer that results in a larger mass change upon binding compared to IgG, thereby improving the measurable signal). Notably, Au nanorods, leveraging their anisotropic localized SPR for enhanced field confinement and larger effective surface area, achieved an exceptional 1 pg LoD for anti-DENV E antibodies in serum [87]. This system also demonstrated crucial selectivity against Zika virus (ZIKV) and yellow fever virus (YFV) antibodies, a critical feature for differential diagnosis in co-endemic regions, likely due to both the specific recombinant antigen used and the sensitive signal transduction.

While Au-based systems provide stability and have shown success, particularly Au nanorods for highly sensitive and specific antibody detection, pushing direct viral antigen LoDs into the sub-ng/mL range in clinical samples remains a challenge. Ag's superior plasmonic properties are attractive but require robust stabilization strategies for practical use.

4.1.2 | Other Promising Nanomaterials

To transcend the limitations of traditional noble metal nanostructures, advanced materials and computational strategies are being integrated into SPR platforms.

4.1.2.1 | Quantum Dots. *Mechanism and properties:* QDs, semiconductor nanocrystals with high refractive indices, primarily act as mass-enhancing labels in SPR, increasing the refractive index change per binding event [183]. In hybrid systems, such as those developed for DENV RNA detection, the interaction is more sophisticated [93]: QD-AuNP–DNA probe conjugates designed in a "closed-loop" structure undergo a conformational change upon target RNA hybridization. This change alters the precise inter-nanomaterial distance, modulating the AuNP's localized SPR through near-field coupling effects, which is then detected as an SPR shift.

TABLE 2 | Key studies on fluorescence-based optical biosensors for detecting DENV using nanotechnology.

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
Chan	2018	AgNC	DENV cDNA	DENV1–4	100 nM	100–500 nM	300 min	Cell culture media	No	[115]
Mok	2021	Aptamer (G-quadruplex)	DENV NS1	DENV2	8.13 nM	2.81–360 nM	30 min	NS1-spiked human serum	No	[116]
Kwon	2020	Aptamer (DNA star)	DENV E	DENV2	1000 PFU/mL	100–10^6 PFU/mL	NA	E-spiked human serum	No	[117]
Fletcher	2010	Aptamer	DENV ssDNA	DENV1–4	NA	NA	20 min	Synthetic ssDNA	No	[118]
Lee	2020	GOx-PNA	DENV ssDNA	DENV1–4, ZIKV	2.1 nM	2.1×10^1–5.1×10^2 FFU/mL	60 min	ssDNA-spiked human serum	No	[119]
Kanagavalli	2020	GOx-Ru(II)	DENV NS1	DENV	0.48 ng/mL	0.001-100 μg/mL	< 30 min	NS1-spiked human serum	Yes[b]	[120]
Hein	2025	MMS	Anti-DENV E Ab	DENV1–4	94.9/97.1%[c]	0.001–1000 ng/mL	NA	Human serum samples	No	[121]
Anderson	2019	MMS	DENV NS1	DENV1–4	NA	64 pg/mL–1 μg/mL	> 75 min	Human serum samples	No	[122]
Tyson	2019	MMS	Anti-DENV NS1 Ab	DENV1–4, ZIKV, WNV	94.3/97.2%[c]	NA	150 min	Human serum/ plasma samples	No	[123]
Gaylord	2015	MMS	Anti-DENV Ab	DENV	10^7 dilutions	100–10^7 dilutions	NA	Anti-Ab commercial plasma	No	[124]
Hosseini	2014	MS	DENV E	DENV2	NA	NA	NA	E recombinant protein	No	[125]
Ortega	2016	SPION	Anti-DENV NS1 Ab	DENV1–4	31.1 ng/mL	0–100 μg/mL	180 min	Human serum samples	No	[126]
Mahmud	2025	Nanoporous AAO	DENV ssDNA	DENV2	0.029 nM	5–1000 nM	> 120 min	Synthetic ssDNA	No	[127]
Melpignano	2016	PS	Anti-DENV NS1 Ab	DENV1–4	NA	NA	30 min	Human serum samples	Yes	[128]
Linares	2013	PSNP	DENV NS1	DENV	5.2 ng/mL	2–100 ng/mL	60 min	Human serum samples	Yes	[129]
Tran	2021	QD	DENV NS1	DENV	0.048 ng/mL	1 pM–120 nM	> 25 min	NS1-spiked human serum	Yes[b]	[130]
Ranzoni	2015	QD-PSNP	DENV NS1	DENV1-4	0.2 ng/mL	1 pg/mL–10 μg/mL	> 60 min	NS1-spiked human serum	No	[131]
Shen	2015	QD	DENV RNA	DENV1–4	0.50 fM	0.5–300 fM	> 60 min	Cell culture media	Yes	[132]

(Continues)

TABLE 2 | (Continued)

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
Adegoke	2025	QD-AuNP	DENV NS1	DENV1	100 pg/mL	NA	NA	NS1 recombinant protein	No	[133]
Monday	2023	QD-AuNP	DENV cDNA	DENV3	1.57 nM	1 pM–100 nM	> 30 min	Synthetic cDNA	No	[134]
Adegoke	2017	QD-AuNP	DENV RNA	DENV1–4	31 cp/mL	20–120 cp/mL	NA	Synthetic RNA	No	[135]
Chowdhury	2018	QD-GO-AuNP	DENV ssDNA	DENV1–4	9.4–14.3 fM	1 fM−1 μM	NA	Synthetic ssDNA and clinically isolated DENV3	No	[136]
Zavoiura	2018	QD-PNA	DENV RNA	DENV	10 pM	10 pM−100 nM	300 min	Human plasma samples	No	[137]
Sitthisuwannakul	2024	Au/ZnONW	DENV NS1	DENV1–4	1.35 pg/mL	1.3–6.5 pg/mL	300 min	Human urine samples	No	[138]

Abbreviations: AAO, anodic aluminum oxide; Ab, antibody; AgNC, silver nanocluster; AuNP, gold nanoparticle; AuNW, gold nanowire; cDNA, complementary DNA; cp, DENV-RNA copies; DENV, dengue virus; DNA, deoxyribonucleic acid; E, envelope protein; FFU, focus forming units; GO, graphene; GOx, graphene oxide; LoD, limit of detection; MMS, magnetic microsphere; MS, microsphere; NA, not available; NS1, nonstructural protein 1; PFU, plaque forming units; PNA, peptide nucleic acid; PoC, point-of-care; PS, polystyrene substrate; PSNP, polystyrene nanoparticle; QD, quantum dot; RNA, ribonucleic acid; SPION, superparamagnetic iron oxide nanoparticles; ssDNA, single-stranded DNA; WNV, west Nile virus; ZIKV, zika virus; ZnO, zinc oxide.

[a]For an optical biosensor to be considered a PoC device, it should be affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free, and deliverable to end-users, aligning with the ASSURED criteria set by the WHO.

[b]The optical biosensor is designed as a PoC device, although its immediate implementation in certain settings may be limited without prior preparation.

[c]Sensitivity/specificity values.

TABLE 3 | Key studies on colorimetric-based optical biosensors for detecting DENV.

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
Vinayagam	2018	AgNP	DENV RNA	DENV3,4	NA	NA	~10 min	Synthetic RNA	Yes	[139]
Flores	2025	AuNP	DENV ssDNA	DENV2	36.1 ng/μL	NA	>30 min	Synthetic ssDNA	No	[140]
Cam Duyen	2023	AuNP	DENV RNA	DENV1	1 pg/μL	0–2500 pg/μL	60 min	Human serum samples	No	[141]
Vinayagam	2019	AuNP	DENV cDNA	DENV4	10^{-6} dilutions	10^{-10}–10^{-2} dilutions	10 min	Cell culture media	No	[142]
Khoris	2022	AuNP-aptamer	DENV NS1	DENV2	1.28 pg/mL	100–10^{6} pg/mL	>25 min	NS1-spiked human serum	No	[143]
Basso	2019	AuNP-aptamer-SPION	DENV NS1	DENV1-4	NA	NA	NA	Cell culture media	Yes[b]	[144]
Rahman	2014	AuNP-PNA	DENV ssDNA	DENV1	0.12 μM	0–12 μM	15 min	Synthetic ssDNA	No	[145]
Dasgupta	2024	Au/AgNPs-SPION	DENV	DENV	2.6 fg/mL	10 fg/mL–100 pg/mL	43 min	Human serum samples	No	[146]
Hosseini	2020	Electrospun FPAP	DENV NS1	DENV2	0.5 pg/mL	5–5×10^{5} pg/mL	NA	NS1-spiked human serum	No	[147]
Hosseini	2016	Electrospun FPAP	DENV C	DENV2	9.9 PFU/mL	3.5×10^{-5}–3.5×10^{-2} PFU/mL	300 min	Cell culture media	No	[148]
Arruda	2024	MNP-aptamer	DENV RNA	DENV	95/100%[c]	NA	~120 min	Human serum samples	Yes[b]	[149]
Farokhinejad	2021	Nanoyeast scFvs	DENV NS1	DENV1-4	250 ng/mL	100 ng/mL–2 μg/mL	NA	NS1-spiked human plasma	No	[150]
Farahmand	2015	PMNM	DENV E	DENV2	117 PFU/mL	3.5×10^{-2}–3.5×10^{6} PFU/mL	NA	E-spiked human serum	No	[151]
Ramírez-Navarro	2020	SPION	DENV NS1	DENV2	NA	0.415–1.24 μg/mL	NA	Cell culture media	No	[152]
Lin	2025	UiO-66(Ce)-MOF	DENV NS1	DENV2	39.7 pg/mL	0.05–100 ng/mL	85 min	Human samples	No	[153]

Abbreviations: Ab, antibody; AgNP, silver nanoparticle; AuNP, gold nanoparticle; cDNA, complementary DNA; DENV, dengue virus; DNA, deoxyribonucleic acid; E, envelope protein; FPAP, fiber probe analytical platform; LoD, limit of detection; MNP, magnetic nanoparticle; NA, not available; NS1, nonstructural protein 1; PFU, plaque forming units; PMNM, polymer-coated microporous nylon membrane; PNA, peptide nucleic acid; RNA, ribonucleic aciwd; scFvs, single chain fragment variable antibodies; SPION, superparamagnetic iron oxide nanoparticle; ssDNA, single-stranded DNA; UiO, University of Oslo; UiO-66(Ce)-MOF, cerium-based metal–organic framework with UiO-type topology.

[a]For an optical biosensor to be considered a PoC device, it should be affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free, and deliverable to end-users, aligning with the ASSURED criteria set by the WHO.

[b]The optical biosensor is designed as a PoC device, although its immediate implementation in certain settings may be limited without prior preparation.

[c]Sensitivity/specificity values.

TABLE 4 | Key studies on SERS- and luminescence-based optical biosensors, as well as other systems for detecting DENV.

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
SERS										
Khalil	2025	AgNP	DENV	DENV	92/93.4%[b]	NA	> 30 min	Human serum samples	No	[154]
Shahzadi	2025	AgNP	DENV	DENV	NA	NA	40 min	Human serum samples	No	[155]
Ismail	2024	AgNP	DENV NS1	DENV2	0.001 mg/mL	0.001–0.1 mg/mL	~240 min	NS1-spiked human saliva	No	[156]
Gahlaut	2020	AgNR	DENV NS1	DENV	NA	NA	NA	Human serum samples	No	[157]
Song	2020	AgNR	DENV ssDNA	DENV2	0.49 fM	1 fM–10 nM	330 min	Synthetic ssDNA	No	[158]
Paul	2015	AuNP	DENV E	DENV2, WNV	10 PFU/mL	10–10^4 PFU/mL	30 min	Cell culture media	No	[159]
Mustapa	2025	AuNR-AuNS	Anti-DENV NS1 Ab	DENV1–4	25 fg/mL	25 fg/mL–25 μg/mL	~10 min	Anti-NS1 Ab-spiked human plasma	No	[160]
Farokhinejad	2022	Nanoyeast scFvs-Nanobox-based SERS nanotag	DENV NS1	DENV2	10 pg/mL	1 pg/mL–10 ng/mL	65 min	Cell culture media	No	[161]
Luminescence										
Zhu	2018	Peptides from DENV E	Anti-DENV E Ab	DENV1	85.0/96.4%[b]	NA	90 min	Human urine samples	No	[162]
Arts	2016	Peptides from DENV NS1	Anti-DENV NS1 Ab	DENV1	10 pM	5–100 nM	30 min	Anti-NS1 Ab-spiked human plasma	Yes	[163]
Other systems										
García	2017	AuNP	Anti-DENV E Ab	DENV2	50 pg/mL	0–10 ng/mL	30 min	Human serum samples	Yes	[164]
Jeningsih	2020	AuNP-MS	DENV cDNA	DENV2	10^{-29} M	10^{-21}–10^{-12} M	90 min	Human blood, urine and saliva samples	No	[165]
Mazlan	2019	MS	DENV cDNA	DENV2	0.121 fM	1 fM–1 mM	15 min	Human serum, urine and saliva samples	No	[166]
Jamaluddin	2022	MS (G-quadruplex)	DENV RNA	DENV2	0.447 zM	2 zM–2 μM	30 min	Human blood, urine and saliva samples	No	[167]
Ariffin	2018	NS	DENV cDNA	DENV2	0.2 aM	0.1 fM–0.1 nM	90 min	cDNA-spiked human saliva/urine	No	[168]

(Continues)

TABLE 4 | (Continued)

Author	Year	Nanomaterial	Biorecognition target	DENV/other flavivirus detection	LoD	Detection range	Time to result	Sample type	PoC use[a]	Ref.
Mazlan	2017	SiO_2NP	DENV cDNA	DENV2	1 zM	1 fM–10 pM	30 min	Human serum, urine and saliva samples	No	[169]
Amin	2021	Chitosan	DENV E	DENV2	1 pM	0.1–1 μM	> 45 min	E recombinant protein	No	[170]
Kamil	2019	GOx	DENV E	DENV2	1 pM	0.1–1 nM	> 20 min	E recombinant protein	No	[171]
Kamil	2021	GOx-PAMAM	DENV E	DENV2	1 pM	0.1–1 nM	> 20 min	E recombinant protein	No	[172]
Kamil	2019	PAMAM	DENV E	DENV2	1 pM	0.1–1 nM	> 15 min	E recombinant protein	No	[173]
Ferdous	2024	PCF-Zeonex	DENV	DENV	98.8%[b]	NA	NA	Computational modeling	No	[174]
Alam	2025	Si(PhCNR)	DENV	DENV	899 nm/RIU[b]	NA	NA	Computational modeling	No	[175]
Nasr	2024	SiO_2–PbS	DENV	DENV	146,5 deg/RIU[b]	NA	NA	Computational modeling	No	[176]

Abbreviations: Ab, antibody; AgNP, silver nanoparticle; AgNR, silver nanorod; AuNP, gold nanoparticle; AuNR, gold nanorod; AuNS, gold nanosphere; cDNA, complementary DNA; DENV, dengue virus; DNA, deoxyribonucleic acid; E, envelope protein; GOx, graphene oxide; LoD, limit of detection; MS, microsphere; NA, not available; NS, nanosphere; NS1, nonstructural protein 1; PAMAM, polyamidoamine; PCF, photonic crystal fiber; PFU, plaque forming units; RIU, refractive index unit; RNA, ribonucleic acid; scFvs, single chain fragment variable antibodies; SERS, Surface-enhanced Raman scattering; Si(PhCNR), silicon photonic crystal nanorod; SiO_2NP, silica nanoparticle; SiO_2–PbS, silica-lead sulfide nanocomposite; ssDNA, single-stranded DNA; WNV, west nile virus.

[a]For an optical biosensor to be considered a PoC device, it should be affordable, sensitive, specific, user-friendly, robust and rapid, equipment-free, and deliverable to end-users, aligning with the ASSURED criteria set by the WHO.

[b]Sensitivity/specificity values.

DENV antigen or nucleic acid detection: This RNA detection strategy achieved an 11.4 fM LoD in cell culture supernatants [93]. For protein detection, SPR platforms incorporating CdS-QDs with graphene oxide (GOx), reduced GOx (rGOx), or polyamidoamine (PAMAM) dendrimers (which provide a 3D scaffold for high-density bioreceptor immobilization [184]) detected recombinant DENV E protein with pM LoDs (0.1–1 pM) [94–97].

QD-based SPR can dramatically lower LoDs, especially for nucleic acids, which alone produce weak SPR signals due to their small size. However, the clinical translation of systems using heavy-metal QDs (CdS, CdSeTe) is hindered by toxicity concerns. Moreover, many high-sensitivity demonstrations use recombinant proteins or cell culture supernatants, and their performance/stability in complex clinical matrices for PoC use requires extensive validation.

4.1.2.2 | Graphene. *Mechanism and properties:* Graphene's 2D structure offers an exceptionally large surface area for high-density bioreceptor immobilization. Its unique electronic properties and high refractive index can enhance the underlying Au film's surface plasmon field [185]. Biomolecules can also adsorb onto graphene via π-π stacking or electrostatic interactions, which can be leveraged for sensing or bioreceptor attachment, thereby amplifying the SPR signal upon DENV analyte binding [186].

DENV antigen and host antibody detection: NH_2–rGOx–PAMAM–AuNP composites detected recombinant DENV2 E protein with a 0.08 pM LoD in 8 min [91], demonstrating a synergistic interplay where rGOx provides the sensitive interface, PAMAM ensures efficient antibody conjugation, and AuNPs contribute plasmonically. For antibody detection in human serum, GOx-modified Au layers achieved a 62.5 ng/mL LoD for anti-DENV E antibodies [90], with a >300% signal gain over unmodified systems, directly showcasing graphene's signal amplification capability in complex media.

Graphene enhances SPR sensitivity. However, the consistent fabrication of uniform, defect-free graphene layers and the development of stable, reproducible functionalization protocols that preserve its properties without introducing variability are major manufacturing and application challenges. Managing nonspecific binding on its large, reactive surface is also critical [185, 187].

4.1.2.3 | Computational Modeling. A substantial portion of recent SPR research for DENV detection leverages computational modeling to predictively design sensor architectures [98–114]. These studies theoretically explore how the specific physicochemical properties (dielectric constants, layer thicknesses, nanostructure geometries) of novel materials (e.g., AlN, $BaTiO_3$, black phosphorus, $TiSi_2$, etc.) modulate SPR characteristics (e.g., resonance angle shifts, field enhancement, sensitivity in deg/refractive index units).

Computational modeling is an invaluable tool for accelerating the in silico screening and rational design of next-generation SPR sensors (e.g., by optimizing multi-layer stacks with materials like $BaTiO_3$ [99, 104, 107, 111] or 2D materials like WS_2 [109]). However, these theoretical performance enhancements require rigorous experimental validation with DENV analytes in clinically relevant matrices. The practical, cost-effective, and scalable fabrication of these often complex nanostructured interfaces remains a significant translational hurdle from theory to real-world application.

4.2 | Fluorescence-Based Biosensors

Fluorescence-based biosensors are among the most widely employed optical methods for DENV detection due to their potential for high sensitivity and accuracy [188, 189]. These sensors operate by utilizing fluorophores, molecules that absorb light at a specific wavelength and re-emit it at a longer wavelength. Changes in fluorescence intensity, lifetime, or polarization upon the interaction of the DENV analyte with its binding bioreceptor indicate the presence and concentration of the target [190, 191]. Compared to techniques like colorimetry or SPR, fluorescence-based assays often achieve lower LoDs, making them particularly effective for early-stage diagnosis where analyte concentrations are minimal. Nanomaterials play a critical role in these biosensors by enhancing fluorescent signals, improving photostability, enabling novel sensing mechanisms (e.g., Förster Resonance Energy Transfer [FRET]), or facilitating efficient bioreceptor immobilization. Key advancements are summarized in Table 2.

4.2.1 | Quantum Dots

QDs are semiconductor nanocrystals renowned for their exceptional photophysical properties, offering advantages over traditional organic fluorescent dyes in biomedical applications, including DENV detection [192].

Mechanism and properties: QDs exhibit broad absorption spectra (allowing excitation with a single light source for multiplexing), narrow, size-tunable emission peaks (reducing spectral overlap), high quantum yields (brighter signals), and remarkable photostability (resisting photobleaching during prolonged measurements). These properties collectively lead to improved signal-to-noise ratios and enhanced sensitivity for detecting DENV nucleic acids [132, 134–137] or proteins like NS1 [130, 131, 133]. The surface of QDs can be readily modified and conjugated with various bioreceptors (DNA probes, peptide nucleic acids [PNAs], antibodies) to target DENV components specifically. QDs are excellent FRET donors or acceptors [134]. FRET is a distance-dependent, nonradiative energy transfer process between a donor fluorophore and an acceptor (which can be another fluorophore or a quencher like AuNPs). In biosensors, FRET is commonly used by designing systems where the binding of an analyte changes the distance between a QD and its FRET partner [193]. This can lead to two types of "signal-on" responses: either the analyte brings the QD and the acceptor close together, triggering FRET and emission from the acceptor, or it separates them, stopping FRET and restoring the QD's fluorescence, for example, by removing a quencher. Optimizing FRET efficiency relies on controlled geometry and proximity between the nanostructures, which can be challenging

DENV nucleic acid detection: Systems conjugating QDs with DNA probes [132, 137], often in conjunction with AuNPs as quenchers [134–136], have been developed. For instance, carbon QDs-AuNP conjugates, and *N*,*S*-graphene QDs combined with AuNPs have been explored [134, 136]. A highly sensitive system using CdSeS/ZnS-QDs achieved an LoD of 0.5 fM for DENV RNA in cell culture supernatants within ~1 h [132], leveraging a duplex-specific nuclease enzyme to degrade hybridized targets and amplify the signal. Molecular beacon probes, which maintain QDs and AuNPs in close proximity in an inactive "off" state (quenched) and separate upon target binding to an "on" state (fluorescent), offer advantages by optimizing FRET efficiency and reducing background without the need for washing steps. Such a system using CdSe/ZnSeS-QDs conjugated with AuNPs and molecular beacons reported an exceptionally low LoD of ~0.05 fM (31 RNA copies/mL) in synthetic samples [135]. QDs functionalized with PNAs, which offer greater stability and stronger, more specific binding to target nucleic acids than DNA probes [194], achieved a LoD of 10 pM in human plasma samples [137], a significant result given that most DNA-probe systems used synthetic or cell culture supernatants.

DENV antigen detection (NS1): Various strategies include CdZnSeS/ZnS-QDs combined with AuNPs (a FRET-based approach) [133], streptavidin-conjugated QDs (for sandwich immunoassays) [130], and "papaya particles" (QDs embedded in polystyrene NPs, offering signal amplification due to multiple QDs per particle) [131]. Streptavidin-conjugated QDs proved highly sensitive, achieving a LoD of 0.048 ng/mL for NS1 in spiked samples within 25 min [130], while "papaya particles" showed 15-fold higher sensitivity than conventional methods [131].

QD-based fluorescent biosensors, particularly those employing FRET mechanisms with AuNPs or nuclease-assisted signal amplification, have demonstrated extremely low LoDs, especially for DENV nucleic acids. This makes them highly relevant for early diagnosis. However, several challenges persist. Proper surface modifications are required for water compatibility and direct bioreceptor attachment, often involving complex chemistries that can hinder scalability and reproducibility [195]. Many promising LoDs were obtained using synthetic or spiked samples. Rigorous validation with real-world clinical samples (e.g., serum, saliva, urine) is crucial to assess performance in complex matrices and confirm their PoC applicability. Finally, the use of heavy-metal-containing QDs (e.g., Cd-based) raises significant toxicity and environmental concerns, which are major barriers to their widespread clinical adoption and PoC deployment [196, 197]. Efforts are ongoing to develop less toxic QD alternatives.

4.2.2 | Other Promising Nanomaterials

Besides QDs, other nanomaterials [115, 119–129, 138] and advanced biorecognition elements [116–118] are enhancing fluorescence-based DENV biosensors.

4.2.2.1 | Graphene. *Mechanism and properties:* GOx is an excellent fluorescence quencher due to its broad absorption spectrum and efficient energy transfer capabilities. In biosensors, fluorophore-labeled probes (e.g., DNA, PNA, aptamers) adsorbed onto the GOx surface are quenched [198, 199]. Upon target binding, the probe undergoes a conformational change or is displaced from the GOx surface, restoring fluorescence ("signal-on"). GOx's large surface area also facilitates efficient probe loading [198, 199].

DENV antigen and acid nucleic detection: A GOx biosensor incorporating a Ru-bipyridine complex for NS1 detection achieved an LoD of 0.48 ng/mL in spiked samples within 20 min [120] (though it was less sensitive than the best QD-NS1 systems). Another GOx system combined loop-mediated isothermal amplification with PNA probes for nucleic acid detection [119]; while innovative, this approach is less sensitive than direct QD-RNA detection and involves more complex procedures.

GOx-based quenching platforms are attractive for their simplicity. However, their sensitivity may not match that of optimized QD-FRET systems. Reproducibility can also be an issue, as variations in GOx sheet size and oxidation levels can affect quenching efficiency and probe interaction [199].

4.2.2.2 | Microspheres. *Mechanism and properties:* Microspheres provide a high surface area for immobilizing probes or capturing DENV targets, effectively concentrating the analyte and enhancing signal detection [200–202]. Magnetic microspheres offer the additional advantage of easy separation and washing steps, which reduces the background signal [200–202].

DENV antigen and host antibody detection: Methacrylic microspheres functionalized with anti-DENV E antibodies showed 20-fold higher sensitivity than conventional enzyme-linked immunosorbent assay (ELISA) [125]. Multiplex immunoassays using magnetic microspheres coated with DENV E or NS1 proteins detected anti-DENV antibodies in human serum with $>94\%$ sensitivity and $>97\%$ specificity, outperforming traditional methods [121, 123, 124]. Using single-domain antibodies with SpyTag/SpyCatcher technology on magnetic microspheres further optimized NS1 detection by improving antibody orientation [122].

Microsphere-based assays, especially those utilizing magnetic separation, can improve assay performance and enable multiplexing. However, potential issues include nonspecific binding to the microsphere surface, particle aggregation, and autofluorescence, which can affect sensitivity.

4.2.2.3 | Aptamers as Recognition Elements. Aptamers are short, single-stranded DNA or RNA molecules that fold into specific 3D structures capable of binding targets with high affinity and specificity, akin to antibodies. They offer advantages such as ease of synthesis, stability, and smaller size [203, 204]. Strategies like G-quadruplex structures [116], DNA origami scaffolds [117], or enzyme-linked modular designs [118] aim to enhance sensitivity by optimizing molecular recognition and signal transduction. While promising, aptamer-based sensors can be sensitive to environmental conditions (temperature, pH, ionic strength). Complex aptamer designs can increase fabrication costs [205]. Signal amplification often

remains a bottleneck, necessitating integration with nanomaterials or advanced detection schemes to achieve clinically relevant LoDs.

4.2.2.4 | Other Nanomaterial-Enhanced Systems. Magnetite NPs possess unique magnetic properties. In fluorescence immunoassays, they are primarily used for magnetic separation and concentration of the DENV analyte or analyte-antibody complexes. After binding, an external magnetic field can efficiently isolate these complexes from the bulk sample, reducing matrix interference and background fluorescence [152]. This pre-concentration step effectively increases the local concentration of the target at the detection site. Magnetite NP-based immunoassays have demonstrated fluorescence signals nearly 20-fold stronger than conventional ELISA for serological detection [126], directly attributable to this efficient target enrichment and background reduction.

Polystyrene NPs can be loaded with a high density of fluorescent dyes or QDs within their matrix [129, 131]. In immunospot assays, these NPs serve as highly bright labels. Instead of a single fluorophore per binding event, each NP carries multiple emissive species. This results in signal amplification because each antigen-antibody binding event is tagged with a much brighter entity [206, 207]. Polystyrene also offers good stability and well-established surface chemistry for conjugation with antibodies [208, 209]. Their use in immunospot assays for NS1 (LoD 5.2 ng/mL) improved overall sensitivity and, importantly, resistance to photobleaching compared to individual dye molecules, allowing for more robust and longer-lasting signal acquisition [129].

Au/ZnO nanowires create a 3D nanostructured surface with an extremely high surface-area-to-volume ratio [210]. This dramatically increases the number of available sites for bioreceptor (e.g., antibody) immobilization, leading to a higher capture efficiency for DENV analytes [211]. Moreover, the presence of Au on the ZnO nanowires can lead to plasmon-enhanced fluorescence. If the fluorescent dye used in the immunoassay is in close proximity to the Au nanostructures on the ZnO nanowires. In that case, its fluorescence emission can be amplified due to interactions with the localized surface plasmons of the Au. ZnO itself can also exhibit UV fluorescence, though, in fluorescence-linked immunosorbent assays (FLISA), it primarily acts as the scaffold. These Au/ZnO nanowire platforms exhibited exceptional performance in FLISA, achieving an ultra-low LoD of 1.35 pg/mL for NS1 in urine—4500-fold lower than commercial ELISA kits [138]. This remarkable enhancement is a direct consequence of the synergistic effects of increased antigen capture (due to the high surface area) and potential plasmon-enhanced fluorescence amplification.

These examples highlight the diverse strategies—magnetic concentration (magnetite NPs), intrinsic signal amplification by multi-dye loading (polystyrene NPs), and combined high surface area capture with plasmon-enhancement (Au/ZnO nanowires)—through which nanomaterials can boost the performance of fluorescence-based DENV detection. While demonstrating impressive LoDs, particularly with the Au/ZnO nanowire system in noninvasive samples, simplifying detection protocols and reducing processing times remain critical for true PoC applicability.

4.3 | Colorimetric-Based Biosensors

Colorimetric biosensors offer a highly attractive approach for DENV detection, particularly for PoC applications, due to their potential for rapid, cost-effective analysis and visual readout without the need for sophisticated instrumentation [212]. These sensors rely on generating a visible color change—either through the formation of colored products, alterations in light scattering by NPs, or enzymatic reactions—upon interaction with the analyte [213]. Nanomaterials, especially metallic NPs, are central to many colorimetric strategies due to their unique optical properties that are highly sensitive to their aggregation state or local environment. Key advancements are summarized in Table 3.

4.3.1 | Gold and Silver Nanoparticles

AuNPs and AgNPs are the workhorses of colorimetric biosensing due to their intense, size- and shape-dependent localized SPR, ease of functionalization, and strong interactions with biological molecules [214].

Mechanism and properties: Colloidal AuNPs typically appear red due to their localized SPR absorption in the green region of the spectrum, while AgNPs are often yellow [215]. The core mechanism in many AuNP/AgNP-based colorimetric assays is the analyte-induced aggregation or dispersion of the NPs. When functionalized AuNPs/AgNPs aggregate (e.g., due to cross-linking by a DENV analyte or hybridization of complementary DNA probes attached to different NPs), their localized SPR peaks shift to longer wavelengths (red-shift) due to interparticle plasmon coupling. This results in a visible color change (e.g., red to blue/purple for AuNPs) [214, 216]. Conversely, an analyte might prevent aggregation or cause the dispersion of pre-aggregated NPs, leading to a color change back to that of the dispersed state [217].

The surfaces of AuNPs and AgNPs are readily functionalized with bioreceptors like DNA/PNA probes (for DENV nucleic acids [139–142, 145] or aptamers/antibodies (for NS1 protein [143, 144]). This functionalization is key to conferring specificity. The colorimetric response is highly dependent on the initial size, shape, and concentration of the NPs, as well as their stability against nonspecific aggregation in biological media (often controlled by surface capping agents).

DENV nucleic acid detection: AuNPs and triangular AgNPs conjugated with DNA probes have been used for DENV nuclei acid detection [139–142]. Typically, in the presence of the target nucleic acid, hybridization occurs between probes on different NPs, inducing aggregation and a color change. PNA probes, offering higher binding affinity and stability, have also been used with AuNPs [145]. While many of these systems were validated with synthetic or cell culture samples, one study successfully detected DENV RNA in human serum [141], highlighting progress toward clinical applicability.

DENV protein detection (NS1): Aptamers, with their stability and ease of synthesis [218], are emerging as powerful bioreceptors for NS1. An AuNP-based aptasensor achieved an ultra-low LoD of

1.28 pg/mL for NS1 in spiked human serum, representing one of the most sensitive colorimetric methods reported to date [143]. This high sensitivity likely stems from the aptamer's high affinity and the efficient signal transduction (color change) upon aptamer-NS1 binding inducing AuNP aggregation.

Combining AuNPs with maghemite (γ-Fe_2O_3) enables magnetic separation/pre-concentration of the DENV-AuNP complexes before the colorimetric readout, enhancing detection sensitivity and specificity. Such a system successfully detected all four DENV serotypes without cross-reactivity with ZIKV or YFV [144]. Further advancements integrate bimetallic Au/AgNPs with maghemite [146], leveraging synergistic plasmon coupling between Au and Ag for enhanced optical properties, increased active surface area, and improved magnetic separation, leading to higher sensitivity for DENV detection [219, 220].

AuNP/AgNP-based colorimetric assays offer simplicity, visual readout, and cost-effectiveness. The main challenge lies in achieving consistent sensitivity and reproducibility in complex clinical samples, where matrix components can interfere with NP stability or biorecognition. While visual detection is convenient for PoC, objective quantification (e.g., using smartphone cameras or portable spectrophotometers) is often needed for precise results [221–224]. Validating these systems with a broader range of clinical specimens is crucial.

4.3.2 | Other Promising Nanomaterials

Beyond Au/AgNPs, other nanosystems and platform designs are being explored to enhance colorimetric DENV detection.

Inspired by LEGO's modular building block concept, fiber probe analytical platforms integrate electrospun fiber mats into ELISA plate wells [147, 148]. These fiber mats possess a very high surface area, which increases protein (e.g., DENV2 NS1 or C proteins) immobilization capacity compared to standard ELISA wells. The increased surface area for bioreceptor binding and subsequent enzymatic colorimetric reactions leads to an 8- to 12-fold increase in assay sensitivity. This demonstrates how nanostructured (fibrous) platforms can amplify conventional colorimetric (ELISA-like) signals.

Polymer-coated microporous nylon membranes offer a customizable surface for the efficient immobilization of anti-DENV E antibodies, enabling DENV E protein detection via a colorimetric sandwich assay format [151]. The porous nature increases the surface area. Performance can be further enhanced by integrating AuNPs or superparamagnetic iron oxide NPs onto/within the membrane to either catalyze the colorimetric reaction (e.g., AuNPs with peroxidase-like activity) or to pre-concentrate the target.

Magnetite NPs, distinct from maghemite, offer higher magnetization for efficient virus/analyte separation, greater stability under reducing conditions, and easier functionalization. They can be used for the magnetic pre-concentration of DENV NS1 from cell culture supernatants, followed by a colorimetric assay (e.g., ELISA-like) [152]. This approach offers a low-cost, simple method with high specificity. However, the susceptibility of magnetite to oxidation (potentially affecting long-term stability and functionalization integrity) remains a challenge compared to more stable magnetic cores like maghemite.

Yeast cells can be bioengineered to display single-chain fragment variable (scFv) antibodies on their surface (nanoyeasts) [150]. These nanoyeasts act as multivalent biorecognition particles. For DENV NS1 detection, the binding of NS1 to scFv-displaying nanoyeasts can then be detected using a secondary antibody conjugated to an enzyme (like horseradish peroxidase) for a colorimetric readout. This system recognized all four DENV serotypes with a LoD of 250 ng/mL in spiked solutions. Advantages include the potential for high specificity (from the scFv) and biocompatibility. While promising, nanoyeast-based systems face challenges in the complex synthesis and functionalization with scFv antibodies. Sensitivity might be reduced in complex biological samples due to interference or nonspecific binding to the yeast cell surface itself.

Colorimetric biosensors, particularly those employing Au/AgNPs, provide a highly accessible and PoC-friendly platform for DENV detection due to their visual readout and potential for low cost. The core mechanism relies on analyte-induced changes in NP-localized SPR and their aggregation state. Hybrid systems incorporating magnetic NPs enhance sensitivity by enabling pre-concentration. Innovations like fiber probe analytical platforms and nanostructured membranes amplify signals by increasing the surface area for biorecognition. While simple and often rapid, key challenges for colorimetric sensors include achieving robust sensitivity and specificity in complex clinical matrices, ensuring the stability of NP dispersions, and transitioning from qualitative/semi-quantitative visual readouts to reliable quantitative measurements for precise clinical decision-making.

4.4 | SERS-Based Biosensors

SERS is an ultrasensitive vibrational spectroscopy technique that dramatically enhances the Raman signal of molecules adsorbed on or in close proximity to nanostructured metallic surfaces, typically Au or Ag [26, 225]. This enhancement, which can be many orders of magnitude (up to 10^{10}–10^{14}), arises primarily from electromagnetic enhancement (due to localized SPR excitation) and, to a lesser extent, chemical enhancement (charge-transfer mechanisms) [226–228]. SERS provides a unique "fingerprint" spectrum for the analyte, offering high specificity. Its potential for multiplexing and high sensitivity makes it a promising tool for DENV detection, although challenges in reproducibility and substrate fabrication persist. Key advancements are summarized in Table 4.

4.4.1 | Gold and Silver Nanostructures

Au and Ag nanostructures, in various morphologies like NPs and nanorods, are the primary materials used to generate the SERS effect.

Mechanism and properties: The core SERS mechanism relies on the excitation of localized SPR in these metallic nanostructures

by incident laser light [229]. This creates highly localized and intense electromagnetic fields ("hot spots"), particularly in interparticle gaps or at sharp nanostructure features. Molecules situated within these hot spots experience a massive amplification of their Raman scattering cross-section [229]. The SERS enhancement factor is strongly dependent on the nanomaterial's size, shape, aggregation state, and dielectric environment.

For DENV detection, these nanostructures are either functionalized with bioreceptors (e.g., antibodies against NS1) to capture the analyte directly on the SERS-active surface, or they are used as SERS "tags" (NPs functionalized with a Raman reporter molecule and a bioreceptor) in sandwich-type assays [230]. Ensuring that the DENV analyte or the Raman reporter is precisely positioned within the SERS hot spots is critical for achieving maximum signal enhancement. Ag generally provides stronger SERS enhancement than Au, especially with common laser excitation wavelengths (e.g., 532 nm, 633 nm) [231]. However, Au offers superior chemical stability and biocompatibility, and its localized SPR can be tuned to the near-infrared region, reducing background fluorescence from biological samples.

DENV antigen/virus detection: AuNPs conjugated with anti-DENV NS1 antibodies have been used to detect DENV and other flaviviruses (like West Nile virus [WNV]), achieving a LoD of 10 plaque forming units per mL in cell culture supernatants [159]. While promising for early-stage diagnosis, potential cross-reactivity between DENV and WNV due to structural similarities in NS1 is a concern that needs careful management through highly specific antibody selection. The reliance on spiked samples also necessitates further validation in clinical matrices.

Ag nanorod-based SERS biosensors have enabled DENV detection from small volumes (5 μL) of human serum, demonstrating feasibility with portable Raman spectrometers [157]. This is a step towards PoC, but the cost of Raman spectrometers can be a barrier. AgNPs have facilitated direct DENV NS1 protein detection in spiked saliva samples with a LoD of 1 μg/mL [156]. This noninvasive approach is attractive, but again, validation in clinical saliva (which is a complex matrix) and comparison with established LoDs are needed. The relatively high LoD compared to other methods might also limit its utility for very early detection.

DENV acid nucleic and host antibody detection: DNA-based SERS biosensors employing cascaded signal amplification strategies (e.g., localized catalytic hairpin assembly and hybridization chain reaction on SERS substrates) have achieved exceptionally low LoDs of 0.49 fM for DENV acid nucleic targets [158]. These complex amplification schemes, while highly sensitive, add to the assay time and procedural steps. On the other hand, hybrid nanomaterials, such as Au nanorods functionalized with Au nanospheres (creating numerous hot spots), have shown exceptional sensitivity for detecting anti-DENV NS1 antibodies at 25 fg/mL in spiked human plasma [160]. This innovative nanostructuring, which optimizes nanomaterial arrangement and hot spot generation, highlights the potential of SERS for ultrasensitive serological assays.

SERS offers the potential for label-free, highly specific (fingerprint-based), and ultra-sensitive detection. The development of hybrid nanostructures and sophisticated signal amplification strategies for nucleic acids has pushed LoDs to impressive levels. However, several critical challenges hinder widespread clinical translation. Fabricating SERS-active substrates with uniform and highly reproducible enhancement across the surface and from batch to batch is a major hurdle [232–234]. While portable Raman spectrometers exist, their cost and the need for precise laser alignment can limit accessibility, especially for PoC diagnostics in resource-limited settings. SERS signals can be difficult to quantify reliably due to variations in hot spot distribution and analyte orientation. Moreover, biological samples can cause background fluorescence or nonspecific adsorption, interfering with SERS signals.

4.4.2 | Other Promising Nanomaterials

An innovative approach coupled bioengineered nanoyeasts (displaying scFv antibodies against DENV2 NS1) with SERS-active "nanoboxes" (hollow metallic nanostructures with internal hot spots) [161]. The nanoyeasts capture the NS1, and this complex is then brought into proximity with the SERS nanoboxes for signal readout. This system demonstrated high specificity for DENV2 NS1, achieving a LoD of 10 pg/mL in cell culture supernatants. A key advantage was its ability to distinguish DENV2 from other serotypes and ZIKV, addressing the crucial need for specific diagnostics. While highly specific, this approach faces practical limitations. Engineering nanoyeasts with scFv antibodies is technically challenging. Coupling two distinct nano-entities (yeast and nanobox) adds complexity to the assay protocol and may hinder large-scale production and field deployment [235]. Nonspecific biomolecule interactions in real-world samples could also reduce sensor performance [235].

To overcome the limitations of expensive instrumentation and substrate fabrication, research is moving towards developing low-cost alternatives. These include smartphone-based Raman systems (using the phone's camera as a detector and its processing power) and disposable SERS biosensors, such as paper-based SERS platforms [236, 237]. Paper offers a low-cost, flexible, and disposable substrate that can be easily functionalized with SERS-active NPs. Eco-friendly and recyclable SERS substrates, like paper platforms functionalized with green-synthesized NPs or nanocomposite hydrogels, offer sustainable solutions that reduce costs and environmental impact [232–234]. These developments are crucial for making SERS technology more accessible for PoC DENV diagnostics, particularly in resource-constrained settings. However, achieving consistent SERS enhancement and signal reproducibility on these low-cost platforms remains an active area of research.

4.5 | Luminescence-Based Biosensors

Luminescence-based biosensors detect light emitted from a chemical reaction (chemiluminescence) or a biological reaction (bioluminescence) triggered by the presence of the analyte or its interaction with a biorecognition element [238]. These methods offer high sensitivity due to the often very low background signal (as no external light source is required for excitation, unlike in fluorescence). Nanomaterials can play a role in enhancing light output, stabilizing reagents, or serving as

platforms for the luminescent reaction. Key advancements are summarized in Table 4.

Chemiluminescence involves the emission of light from a chemical reaction that produces an electronically excited intermediate, which then decays to a ground state by emitting a photon [239]. Common chemiluminescence systems involve reactions like luminol oxidation catalyzed by horseradish peroxidase in the presence of hydrogen peroxide [240]. In DENV biosensors, this is typically applied in an immunoassay format where one of the antibodies (or the antigen) is labeled with horseradish peroxidase. An assay using DENV E peptides (as immobilized antigen) to detect anti-DENV E antibodies in human urine samples employed a chemiluminescent readout (a horseradish peroxidase-conjugated secondary antibody) [162]. This system demonstrated 85% sensitivity and 96.4% specificity, with results within 90 min. The ability to use noninvasive samples is an advantage, simplifying diagnostics. Chemiluminescence offers high sensitivity due to its low background. However, chemiluminescence reactions can be sensitive to environmental factors (pH, temperature, presence of quenchers, or inhibitors in the sample matrix) [241, 242]. For PoC applications, the need for stable reagents and, often, specialized plate readers for quantitative measurement can be limitations, though visual or simple photodetector readouts are possible for qualitative tests. The requirement for controlled pH conditions might restrict its use in decentralized settings.

Bioluminescence is light produced by living organisms through enzyme-catalyzed reactions, most commonly involving luciferases (e.g., firefly luciferase, NanoLuc) and their substrates (e.g., luciferin, furimazine) [243]. These systems offer stable reagents, often simple readout, and ease of interpretation [244]. Bioluminescence resonance energy transfer (BRET) is analogous to FRET but uses a bioluminescent donor (e.g., a luciferase) instead of a fluorescent one [245, 246]. Energy is transferred nonradiatively from the excited product of the luciferase reaction to a nearby fluorescent acceptor protein (e.g., mNeonGreen) if they are within ~10 nm. The binding of a DENV analyte can bring the luciferase and acceptor protein together or separate them, modulating the BRET signal [247]. A BRET-based biosensor enabled rapid (30 min), label-free detection of anti-DENV NS1 antibodies, even in undiluted samples [163]. This system, composed of NanoLuc (donor) and the fluorescent protein mNeonGreen (acceptor) linked via components that interact upon antibody binding, achieved pM sensitivity. A key advantage was its adaptability for smartphone-based analysis, demonstrating PoC potential. The modular design also allowed for adaptation to detect other viruses like human immunodeficiency virus, showcasing its versatility. Bioluminescent sensors, especially NanoLuc-based systems, are extremely sensitive due to the high quantum yield of the luciferase and very low background signals [248, 249]. BRET adds another layer of specificity and allows for ratiometric measurements (ratio of acceptor to donor emission), which can reduce variability. However, a primary challenge for bioluminescent biosensors is enzyme stability (luciferase activity can degrade over time or under harsh conditions), which can affect sensor shelf-life and widespread application [250, 251]. The availability and cost of specific substrates (like furimazine for NanoLuc) can also be a consideration.

While inherently sensitive, detecting very low concentrations of DENV analytes (e.g., early-stage anti-DENV antibodies or low viremia) remains critical. Nanomaterial-based signal amplification strategies could be key [252, 253]. Optimizing biorecognition elements (e.g., advanced peptide sequences, aptamers) to enhance target binding specificity and reduce cross-reactivity is crucial [254]. Developing novel, more stable, and brighter bioluminescent probes (e.g., engineered luciferases, high-efficiency luminescent dyes) can improve quantum yield and signal-to-noise ratios [251, 255]. Designing simpler detection platforms that reduce reliance on specialized equipment (e.g., integrating with microfluidics or paper-based devices) is essential for PoC translation. Integrating deep learning or artificial intelligence for improved data analysis and results interpretation can enhance accuracy and user-friendliness [235].

4.6 | Other Optical Systems

Beyond the major categories previously discussed, several other innovative optical systems have been developed or adapted for DENV detection, often leveraging unique light-matter interactions or specialized optical components. These include reflectance-based sensors [165–169], interferometric methods [170–176], and caustic light scattering technologies [164], each with distinct mechanisms and potential applications (Table 4).

4.6.1 | Tapered Optical Fibers for Interferometric Methods

Tapered optical fibers (TOFs) are optical fibers with a gradually reduced diameter in a specific sensing region. This tapering enhances the evanescent wave—the portion of the guided light that extends into the surrounding medium—allowing for a much stronger interaction with analytes bound to the fiber surface compared to standard optical fibers [256–258]. When DENV analytes (e.g., E protein) bind to bioreceptors (e.g., anti-DENV E antibodies) immobilized on the tapered region, they alter the effective refractive index experienced by the evanescent wave. This change in refractive index causes a shift in the interference pattern of light propagating through the fiber, which can be measured as a change in transmitted light intensity or wavelength [259]. The sensitivity of TOFs arises from this enhanced light-analyte interaction and the inherent sensitivity of interferometric measurements to minute refractive index changes.

Nanomaterials are integrated onto the TOF surface primarily to increase the bioreceptor loading capacity or further modulate the local refractive index upon analyte binding. PAMAM dendrimers, highly branched, 3D polymers, provide an increased surface area and multiple functional groups for the covalent attachment of a higher density of anti-DENV E antibodies [173]. This increased antibody density enhances the probability of capturing DENV E protein, leading to a larger overall refractive index change. GOx, with its large surface area and oxygen-containing functional groups, can also serve as an effective platform for antibody immobilization [171]. Moreover, its high refractive index can

contribute to a greater shift in the evanescent wave properties upon protein binding. Combining GOx and PAMAM aims to synergize their benefits—the high surface area and potential electronic contributions of GOx with the 3D scaffolding and functional group density of PAMAM—for even more efficient antibody immobilization and signal transduction [172].

TOF sensors functionalized with anti-DENV2 E antibodies and enhanced with PAMAM dendrimers, GOx, or GOx–PAMAM complexes have achieved LoDs for DENV E protein of around 1 pM within approximately 20 min, outperforming standard biofunctionalized fibers [171–173]. This LoD, while good, is still an order of magnitude higher (less sensitive) than those achieved by some of the best SPR-based biosensors using AuNPs or QDs for protein detection, suggesting a comparatively lower intrinsic sensitivity for this TOF configuration.

TOFs offer advantages like relatively simple fabrication and the potential for miniaturization. The integration of nanomaterials clearly improves their performance by increasing bioreceptor density. However, achieving ultrahigh sensitivity comparable to advanced SPR or fluorescence methods remains a challenge. Ensuring robust and reproducible tapering and surface functionalization are also key for reliable performance.

4.6.2 | Reflectance

These sensors typically measure changes in light scattered or reflected from a surface where DENV nucleic acid (cDNA or RNA) hybridization occurs [165–169]. The interaction often takes place on the surface of microspheres or specialized substrates. An additional layer or optical markers (like AuNPs) are frequently incorporated to enhance specificity and the magnitude of the reflectance change [260].

Acrylic microspheres, for example, can be functionalized to immobilize DNA probes specific for DENV cDNA or RNA [166, 167]. Latex-AuNPs can serve as optical markers in sandwich hybridization assays. The presence and density of these AuNPs, bound due to target hybridization, alter the reflectance properties of the surface [165]. Porous silica nanospheres can also act as matrices for immobilizing DNA probes, offering a high internal surface area [168].

Reflectance-based systems have demonstrated extraordinary sensitivity for DENV nucleic acid detection. Acrylic microspheres with immobilized DNA probes detected DENV2 cDNA with a LoD of 0.121 fM in just 15 min [166]. A G-quadruplex DNA probe on acrylic microspheres, hybridizing with DENV2 RNA, achieved a remarkable LoD of 0.447 zM (zeptomolar, equivalent to 4.47×10^{-7} fM) in 30 min [167]. This extreme sensitivity likely arises from specific structural changes in the G-quadruplex upon RNA binding that lead to a highly detectable optical signal, possibly amplified by the microsphere platform. A sandwich hybridization strategy on acrylic microspheres functionalized with succinimide, using latex-AuNPs as optical markers, reported a LoD of 10^{-29} M for DENV cDNA [165]—the lowest ever detected by any method reviewed. This unprecedented sensitivity suggests a highly efficient capture and signal generation mechanism, where even a few binding events are amplified by the AuNP markers. Aminated porous silica nanospheres for cDNA detection achieved an LoD of 0.2 aM (attomolar, 0.0002 fM) [168]. The extreme sensitivity of this system arises from several synergistic factors attributed to the porous silica nanospheres: (i) an exceptionally high internal surface area allowing for a vastly increased density of immobilized DNA probes, thereby maximizing target capture probability; (ii) potential nanoconfinement effects within the pores, concentrating hybridization events; and (iii) complex light-matter interactions where the nanostructured porous matrix, laden with hybridization complexes, leads to amplified and highly sensitive changes in the overall surface reflectance.

Illustrating further advancements in reflectometric sensitivity, a solid-state DNA optode employed aminated silica nanoparticles (SiO_2NPs) as a stable matrix for covalently immobilized DNA probes [169]. Detection of DENV2 cDNA was achieved using a Zn–salphen complex as an optical label. The detection mechanism relies on target cDNA hybridization to the immobilized probes, creating dsDNA into which the planar, aromatic Zn–salphen complex intercalates via π-stacking interactions. This intercalation induces a distinct color change on the SiO_2NP surface, quantitatively measured as a decrease in light reflectance. This strategy yielded an exceptional LoD of 1 zM within 30 min, with high selectivity against single nucleotide mismatches. The remarkable zM sensitivity stems from the combination of efficient surface hybridization on the nanoparticles and the significant optical signal change generated by even minimal intercalation of the Zn–salphen complex, effectively transducing few molecular binding events into a measurable reflectometric signal.

Importantly, many of these ultra-sensitive reflectance systems have been validated for use with clinical samples like blood, urine, and saliva, making them highly promising for early and noninvasive DENV detection. The mechanisms behind such extreme sensitivities (zeptomolar, 10^{-29} M) likely involve a combination of highly efficient probe-target hybridization, signal amplification from NP markers, and potentially unique optical phenomena occurring on the microsphere/nanosphere surfaces. Despite their remarkable sensitivity, challenges remain for their integration into field-based PoC diagnostics. These include the potential high cost of specialized reagents (e.g., highly purified probes, G-quadruplexes), complexity in fabricating reproducible sensor surfaces (e.g., uniform microsphere coatings), and often, the requirement for specialized optical readers for quantitative data acquisition, which may limit their widespread application in resource-limited settings.

4.6.3 | Optical Caustic Plasmonic Light Scattering

This approach, demonstrated by García et al. [164], measures changes in green light scattering from 60 nm AuNPs using an "optical caustic focus." DENV E protein is conjugated to the AuNPs. Patient antibodies (anti-DENV E antibodies) cross-link these functionalized AuNPs, inducing aggregation. This aggregation alters the solution's light scattering properties due to interparticle plasmon coupling, which is sensitively detected by the optical caustic setup (lens-free and light-emitting diode-based). The feasibility study showed good agreement with dot blot for 10 human serum samples, indicating promise for

detecting AuNP aggregation in a homogeneous assay format. This represents an innovative, potentially low-cost light scattering method. Key advantages are its homogeneous format and potential for portable instrumentation. Further optimization for clinical sensitivity/specificity and matrix effects is needed.

5 | Comparative Analysis and Discussion

Several well-established methods are available for detecting DENV, including reverse transcription polymerase chain reaction (RT-PCR) for DENV RNA, serological tests such as ELISA, and NS1 protein assays [261], with PCR often considered the gold standard. Table 5 summarizes the performance of some commercially available NS1 diagnostic kits, antibody serology kits, and PCR kits for DENV detection [262–266] and compares them with five optical biosensors discussed in this review.

A key factor in assessing conventional methods is their ability to detect biomarker concentrations relevant to early diagnosis. Early detection is particularly challenging because patients typically present with nonspecific symptoms and undifferentiated fever within 5 to 7 days postinfection. Commercial ELISA kits exist but are generally unsuitable for early diagnosis, as IgM antibodies usually appear 5 to 7 days after symptom onset [267, 268]. This delay complicates result interpretation for acute infections. Additionally, there is a risk of cross-reactivity with other flaviviruses. Detection technologies targeting viral components (nucleic acid or proteins) are especially useful in the early stages before the immune response clears the virus [269]. During the acute phase, DENV RNA is typically found in blood at concentrations of 10^3–10^6 copies/mL [270]. While qRT-PCR can detect as few as 10^3 RNA copies/mL, its effectiveness is limited by the short duration of viremia in most DENV infections, making serological methods a necessary complement. Moreover, PCR remains costly and impractical for routine clinical diagnostics. The NS1 antigen, present across all DENV serotypes, reaches high levels in the early days of illness, making it a reliable marker for early diagnosis. It can be detected from day 0, peaking between days 6 and 10 [271, 272] at concentrations ranging from 0.01 to 2 μg/mL [273]. As a result, most commercial diagnostic kits target NS1. Additionally, alternative detection systems focusing on the DENV E protein have been explored, as highlighted in this systematic review. Nanotechnology-based approaches are being investigated to enhance optical biosensors for early DENV detection, addressing the limitations of current commercial diagnostic methods.

5.1 | Evaluating Performance and Economic Feasibility of Nanotechnology-Based Optical Biosensors

Comparing commercial diagnostic methods with biosensors for DENV detection is challenging due to limited data on biosensor specificity and costs. Additionally, biosensors typically report sensitivity as LoD, using highly variable measurement units. Among the reviewed biosensors, only five provide sensitivity and specificity values, allowing direct comparison with commercial kits (see Table 5) [81, 121, 123, 149, 162]. Optical biosensors emerge as a promising alternative, offering high sensitivity (83%–95%) and specificity (96.4%–100%) with processing times ranging from 10 to 150 min, depending on the detection method. Notably, the SPR biosensor developed by Jahanshahi et al. [81] enables rapid detection within just 10 min while maintaining high sensitivity and specificity, outperforming both ELISA and rapid tests in overall efficiency. Moreover, these optical biosensors offer greater flexibility in sample type, allowing DENV detection in serum, plasma, saliva, or urine, thereby expanding their diagnostic applicability.

The economic analysis for the implementation of optical biosensors based on nanotechnology for DENV detection depends on multiple factors, including the synthesis and scalability of nanomaterials, as well as the type of biosensor used. Comparing their cost with current conventional methods is challenging, as existing studies present diverse conclusions [274]. On the one hand, it has been reported that the cost–benefit ratio of rapid diagnostic tests for DENV ranges between $3 and $7, making them cheaper than a DENV-specific ELISA test [275]. However, another study using cost-effectiveness modeling determined that these rapid diagnostic tests were not advantageous, as they were more expensive and less effective than presumptive treatment [276]. Therefore, a comprehensive cost-effectiveness assessment is essential in endemic settings. Such an assessment should consider total costs along with the sensitivity and specificity of novel diagnostic methods to optimize their practical application.

5.2 | Comparing Nanotechnology-Based Optical Biosensor Modalities: Features, Limitations, and PoC Suitability

This systematic review describes a diverse group of nanotechnology-enabled optical biosensors for DENV detection, each employing different transduction mechanisms with inherent strengths and weaknesses. A comparative analysis reveals distinct trends regarding sensitivity, speed, complexity, and suitability for PoC applications (Table 6). Notably, techniques such as SERS and some reflectometric or interferometric methods achieved the highest sensitivities reported, detecting DENV nucleic acids down to femtomolar or even lower concentrations [158, 167, 168]. This ultrahigh sensitivity is ideal for early diagnosis when viral loads are minimal. However, this exceptional performance often comes at the cost of longer analysis times (sometimes exceeding several hours) and reliance on specialized, bulky, or expensive equipment (e.g., Raman spectrometers or specialized optical setups), which currently limits their widespread PoC applicability despite their analytical prowess (Table 6).

In contrast, colorimetric and some SPR-based biosensors offer much faster detection times, with several assays providing results within 5 to 15 min [81, 85, 91, 139, 142, 145]. This rapidity is a critical advantage for PoC diagnostics. Nevertheless, this speed is often achieved at the expense of sensitivity, with LoDs for these faster methods generally falling in the ng/mL range, which may be less suitable for detecting very low analyte levels (Table 6). While SPR offers the benefit of label-free, real-time kinetic analysis, its broader PoC

TABLE 5 | Comparison of commercial and optical biosensors-based diagnostic tests for DENV.

Test principle	Target	Product name	Sensitivity (%)	Specificity (%)	Time (min)	Sample type
Commercial diagnostic tests						
ELISA	DENV NS1	InBios DENV Detect NS1 ELISA	95.9–100	99.2–100	110	Human serum samples
		Euroimmun Dengue virus NS1 ELISA	100	99.2	111–135	Human serum and plasma samples
		Platelia Dengue NS1 Ag Kit, Biorad	83.6–89.4	97.4–98.7	140	Human serum samples
		Pan-E Dengue Early ELISA, Panbio	72.3–85.5	95.5–100	160	Human serum samples
		SD Dengue NS1 Ag ELISA	76.7	98.3	160	Human serum and plasma samples
	Anti-DENV IgM Ab	InBios DENV Detect IgM capture ELISA	88.7–92.0	93.1–97.3	90–196	Human serum samples
		Abcam Anti-Dengue virus IgM Human ELISA kit	81.0	88.7	105	Human serum and plasma samples
		Euroimmun Anti-Dengue virus ELISA (IgM)	38.1	100	75	Human serum and plasma samples
		Dengue Fever Virus IgM Capture, Focus Diagnostics	98.6	79.9	225	Human serum samples
		Pathozyme M Dengue (and Capture), Omega	61.5–83.5	84.6–86.5	110–120	Human serum and plasma samples
		Dengue IgM Capture, Panbio	87.6–89.5	86.1–88.1	130	Human serum samples
		SD Dengue IgM Capture, Standard Diagnostics	84.9	97.3	130	Human serum and plasma samples
	Anti-DENV IgG Ab	InBios DENV Detect IgG ELISA	97.1	97.7	136	Human serum samples
		Abcam Anti-Dengue virus IgG Human ELISA kit	100	89.7	105	Human serum and plasma samples
		Euroimmun Anti-Dengue virus ELISA (IgG)	94.3	98.5	75	Human serum and plasma samples
		Panbio Dengue Virus IgG Capture ELISA, Abbott	56.0	95.0	130	Human serum and plasma samples
Rapid Test	DENV NS1	Asan Easy Test Dengue NS1 Ag 100	42.9	99.2	15–20	Human serum, plasma and whole blood samples
		Standard Diagnostics, SD BIOLINE Dengue Duo	57.1–87.0	73.4–100	15–20	Human serum, plasma and whole blood samples
		Boditech Med ichroma Dengue NS1	64.3	100	15–20	Human serum, plasma and whole blood samples
		Dengue NS1 Detect, Inbios	76.5–86.0	97.4–100	30	Human serum samples

(Continues)

TABLE 5 | (Continued)

Test principle	Target	Product name	Sensitivity (%)	Specificity (%)	Time (min)	Sample type
		Biorad NS1 Ag Strip	72.8–79.1	100	15–30	Human serum samples
		Panbio NS1 Ag Strip	71.9	95	15	Human serum samples
	Anti-DENV IgM Ab	Asan Easy Test Dengue IgG/IgM	41.3	100	15–20	Human serum, plasma and whole blood samples
		Standard Diagnostics, SD BIOLINE Dengue Duo	49.2–87.3	86.8–98.7	15–20	Human serum, plasma and whole blood samples
		Boditech Med ichroma Dengue IgG/IgM	85.7	92.0	15–20	Human serum, plasma and whole blood samples
		Panbio Dengue Duo Cassette (IgM/IgG)	77.8–92.1	62.2–90.6	15	Human serum samples
		Hapalyse dengue-M PA kit, Pentax	97.7	76.6	90	Human serum samples
		Dengue check WB, Zephyr (IgM/IgG)	20.5	86.7	15	Human serum samples
	Anti-DENV IgG Ab	Asan Easy Test Dengue IgG/IgM	65.7	100	15–20	Human serum, plasma and whole blood samples
		Standard Diagnostics, SD BIOLINE Dengue Duo	71.4–89.0	64–100	15–20	Human serum, plasma and whole blood samples
		Boditech Med ichroma Dengue IgG/IgM	94.3	98.5	15–20	Human serum, plasma and whole blood samples
qRT-PCR	RNA	RealStar Dengue, Altona Diagnostics	90.3	100	120–180	Human serum samples
		GenoAmp Trioplex, MEDIVEN	90.3	83.9	120–180	Human serum samples
		GenoAmp Dengue, MEDIVEN	100	100	120–180	Human serum samples
Optical biosensors-based diagnostic tests						
Jahanshahi [81]	Anti-DENV IgM Ab	SPR	83	100	10 min	Human serum samples
Hein [121]	Anti-DENV E Ab	Fluorescent	94.9	97.1	NA	Human serum samples
Tyson [123]	Anti-DENV NS1 Ab	Fluorescent	94.3	97.2	150 min	Human serum and plasma samples
Arruda [149]	DENV RNA	Colorimetric	95	100	~120 min	Human serum samples
Zhu [162]	Anti-DENV E Ab	Luminiscent	85.0	96.4	90 min	Human urine samples

Abbreviations: Ab, antibody; DENV, dengue virus; E, DENV envelope protein; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; NS1, nonstructural protein 1; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RNA, ribonucleic acid; SPR, surface plasmon resonance.

TABLE 6 | Comparative overview of nanotechnology-enabled optical biosensing modalities for DENV.

Optical modality (No.)	Predominant nanomaterial (s)	Target analyte (s) commonly detected	Reported LoD[a]	Time-to-result range[a]	Typical sample types	Intrumentation requeriment/ complexity[b]	PoC potential[c]	Key advantages/ llimitations
SPR (36)	Au nanostructures and QDs	E, NS1 Anti-DENV Ab	E: 0.08–1 pM NS1: 60–74 ng/mL	5–120 min	Human (plasma/serum) Synthetic Computational modeling	Specialized SPR equipment (moderate to high)	Low to moderate	–Label-free –Real-time kinetics –Good sensitivity –Expensive/bulky setup –Surface fouling –Limited throughput
Fluorescence (24)	QDs (often with AuNPs)	NS1 NAc	NS1: 1.3–5200 pg/mL NAc: 0.50 fM–100 nM	20–300 min	Human (plasma/serum) Spiked Synthetic	Fluorometer/ Microscope (low to moderate)	Moderate to high	–High sensitivity –Multiplexing-capable –Probe versatility –Photobleaching – Autofluorescence –Requires labels/ enzymes
Colorimetry (15)	AuNPs	NS1 NAc	NS1: 0.2 pg/ mL–250 ng/mL NAc: 1 pg/μL–0.12 μM	10–300 min	Spiked Cell culture Human (serum)	Visual or simple reader (low)	High	–Low cost, simple, rapid –Visual readout –Lower sensitivity versus SPR/SERS –Subjective quantification
SERS (8)	Au, Ag nanostructures	NS1	0.49 fM-10 pg/ mL–0.001 mg/mL	10–330 min	Spiked Cell culture	Raman spectrometer (moderate to high)	Low to moderate	–Ultrahigh sensitivity –Molecular fingerprinting –Reproducible substrates –Expensive/ specialized setup –Signal variability
Luminescence (2)	Specific peptides	Anti-DENV Ab	10 pM	30–90 min	Human (urine) Spiked	Plate reader, smartphone (Low to moderate)	Moderate	–Good sensitivity –Noninvasive sampling –Enzyme stability –pH dependence

(Continues)

TABLE 6 | (Continued)

Optical modality (No.)	Predominant nanomaterial (s)	Target analyte (s) commonly detected	Reported LoD[a]	Time-to-result range[a]	Typical sample types	Intrumentation requeriment/ complexity[b]	PoC potential[c]	Key advantages/ limitations
								–Specific reagent needs
Other optical systems (13)	AuNPs, GOx, PAMAM, micro (nano)spheres	NAc E	NAc: 0.4 zM–0.1 fM E: 1 pM	15–90 min	Human (urine, saliva) Synthetic	Fiber optics Custom setups (moderate to high)	Moderate	–Extreme sensitivity –Noninvasive sampling –Complex setup –Limited scalability

Abbreviations: Ab, antibody; Ag, silver; Anti-DENV-Ab, anti-dengue virus antibody; Au, gold; AuNPs, gold nanoparticles; DENV, dengue virus; E, dengue virus E protein; GOx, graphene oxide; LoD, limit of detection; NAc, nucleic acid; No., number of reviewed studies; NS1,dengue virus NS1 protein; NS1, nonstructural protein 1; PAMAM, poly(amidoamine) dendrimer; PoC, point-of-care; QDs, quantum dots; SERS, surface-enhanced Raman scattering; SPR, surface plasmon resonance; zM, zeptomolar.

[a]For LoD and time ranges, the extreme reported values were considered.

[b]A qualitative assessment was performed based on the following: Low (visual detection or very basic, low-cost lab equipment); Moderate (requires standard lab equipment, but not highly specialized or expensive); and High (requires specialized, costly, or bulky instrumentation).

[c]A qualitative assessment was performed based on the following: Low (visual detection or very basic, low-cost lab equipment); Moderate (requires standard lab equipment, but not highly specialized or expensive); and High (requires specialized, costly, or bulky instrumentation).

deployment is hindered by the need for relatively complex and expensive equipment. Colorimetric assays [85, 142, 145], on the other hand, stand out for their simplicity and potential for visual readout, making them strong candidates for low-cost PoC devices, though quantitative accuracy can be a limitation if relying solely on visual interpretation.

Fluorescence-based biosensors appear to strike a more balanced profile between sensitivity and practicality for a range of DENV targets, including nucleic acids and proteins. Many fluorescence assays achieved LoDs in the pM to fM range for nucleic acids [93, 132, 135] and the pg to ng/mL range for NS1 protein, with analysis times typically ranging from under 30 min to over an hour (Table 6). While generally more sensitive than basic colorimetric tests and faster than some SERS protocols, they often necessitate fluorophores, specific reagents, and detection instrumentation (fluorometers or microscopes), which adds layers of complexity and cost compared to the simplest PoC formats. However, the versatility of fluorescent probes and the potential for multiplexing are advantages. Luminescence-based methods, though less represented in this review, also show promise with good sensitivity and the ability to use noninvasive samples but can be limited by factors like enzyme stability or specific reaction condition requirements.

Regarding maturity for PoC applications, colorimetric assays, along with some simpler fluorescence-based tests, seem closest to practical field deployment due to their inherent simplicity, lower cost, and reduced need for extensive equipment. The six fastest biosensors identified in this review, for instance, predominantly utilized AuNPs within SPR or colorimetric frameworks, highlighting the utility of well-established nanomaterials in rapid detection formats. Conversely, modalities like SPR and SERS, despite their impressive analytical performance in laboratory settings, face more substantial hurdles concerning instrument miniaturization, cost reduction, and overall user-friendliness essential for widespread PoC adoption.

The choice of optical biosensing modality for DENV detection involves careful consideration of these compromises: achieving ultrahigh sensitivity may sacrifice speed and PoC-readiness, while rapid and simple tests might not offer the lowest LODs. The integration of nanotechnology has undoubtedly pushed the boundaries of what is achievable for DENV detection across all these optical platforms. However, continued innovation is needed to develop biosensors that optimally balance all the desired characteristics for effective, accessible, and rapid diagnostics, particularly those aligned with the Affordable, Sensitive, Specific, User-friendly, Robust and rapid, Equipment-free, and Deliverable to end-users (ASSURED) criteria for PoC devices [277].

5.3 | Barriers, Regulatory Considerations, and Challenges for Clinical Translation

Despite the promising advancements in nanotechnology-based optical biosensors for DENV detection detailed in this review, several critical barriers must be overcome before they can be widely adopted in clinical practice. These barriers collectively

explain why few of the reviewed studies currently present truly PoC-ready solutions despite their laboratory successes.

One of the main challenges in translating nanotechnology-based biosensors from research to clinical practice is the lack of regulatory approval and standardization [278–282]. It is crucial to note that this is a broader challenge inherent to the entire field of nanomedicine as it strives for clinical translation, not solely confined to nanobiosensors [283–285]. Unlike conventional diagnostic tests, many of these biosensors remain in the experimental phase and have not undergone rigorous regulatory evaluation by agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). The absence of internationally recognized guidelines for assessing their clinical efficacy complicates the approval process. Establishing standardized validation protocols and performance benchmarks is essential to ensure their reliability, sensitivity, specificity, and comparability with existing diagnostic methods, thereby facilitating their widespread adoption.

A major limitation of these biosensors is the lack of sufficient clinical validation. While they often exhibit excellent sensitivity and specificity in controlled laboratory conditions, their performance in real patient samples remains largely untested. Biological matrices such as blood, serum, and saliva contain complex interfering substances that can affect with sensor accuracy [286]. This is a key challenge for PoC devices, which aim for minimal sample preparation. Because many of the reviewed studies performed limited testing with these real-world samples, their suitability for PoC use remains unproven. Moreover, the long-term stability of nanomaterials, biorecognition elements, and overall sensor performance under varied environmental and storage conditions (essential for PoC deployment, particularly in resource-limited settings) was often not rigorously assessed or reported in the reviewed studies. To truly confirm their diagnostic utility and ensure they work reliably for different patients, large-scale clinical trials across multiple centers are essential. Additionally, compliance with Good Manufacturing Practices is crucial for commercialization, as most biosensors have only been tested under controlled conditions [278]. Demonstrating their robustness through rigorous clinical validation is key to facilitating regulatory approval and widespread adoption.

Manufacturing scalability and reproducibility also pose major challenges in the development of nanomaterial-based biosensors. Achieving consistent control over the size, shape, and surface chemistry of nanomaterials is crucial, as small variations in synthesis can significantly impact sensor performance [278]. Additionally, integrating these materials into biosensor platforms must ensure long-term stability and batch-to-batch uniformity, both of which are critical for regulatory approval and large-scale commercialization and, ultimately, the cost-effectiveness required for PoC devices.

From an economic perspective, cost, accessibility, and integration into existing healthcare systems are key challenges for the widespread adoption of biosensors [287]. Many advanced optical biosensors rely on expensive technologies (such as SPR systems, Raman spectroscopy, and fluorescence-based detection) and specialized materials, making the overall cost of the final PoC device a barrier if not addressed from the early development stages. The reviewed studies often lacked detailed cost analysis for potential PoC translation. Additionally, the lack of infrastructure in low-income regions, where DENV is endemic, further limits their implementation. To address these issues, future efforts should focus on developing affordable, scalable, and user-friendly biosensors that require minimal technical expertise while ensuring compatibility with existing diagnostic workflows, including PoC devices, electronic health record systems, and surveillance programs.

Lastly, beyond regulatory concerns, ethical considerations play a crucial role in the deployment of nanotechnology-based biosensors [288]. One major issue is informed consent and patient safety. Since many biosensors are designed for PoC diagnostics [289], ensuring that patients understand the benefits and limitations of these technologies is critical. Moreover, data privacy concerns must be addressed, particularly regarding the secure handling and storage of diagnostic results, which may be integrated into electronic health record systems [224, 290, 291].

Overcoming these challenges will require interdisciplinary collaboration among researchers, clinicians, regulatory agencies, and industry partners to bridge the gap between laboratory research and real-world clinical applications. Ensuring the safe, effective, and equitable use of nanotechnology-based biosensors in diagnostics will be crucial for their successful implementation.

5.4 | Risk of Bias Assessment

A critical aspect of this systematic review was assessing the methodological quality of included studies using the modified CASP checklist. This allowed us to identify key weaknesses and potential biases within them. The inter-reviewer reliability for the risk of bias assessment was good (ICC = 0.81; 95% CI 0.72–0.87).

Among the 98 articles assessed, 35 (35.7%) were of high quality, 60 (61.2%) were of moderate quality, and only 3 (3.1%) were of low quality [95, 106, 114] (Figure 2B and Supplemental File 4). Low-quality studies lacked essential elements for robust clinical application, such as comparison with a well-established reference standard, testing on real clinical samples, and demonstrating a measurable impact of the biosensor's effect on patient needs. Notably, one study [95] did not disclose potential conflicts of interest or commercial funding, raising concerns about possible bias in its the reported findings.

Regarding signaling questions (Figure 2C and Supplemental File 4), almost all articles clearly and adequately addressed the study objectives (Q1, 96.9%).

One of the most significant limitations observed was the lack of validation with clinical samples, as many biosensors were tested only with synthetic samples or spiked solutions rather than real biological matrices. This limitation directly impacts their demonstrable potential for PoC use. Performance in idealized laboratory conditions often fails to translate reliably to real-world clinical settings, where the complexities of diverse patient samples and interfering substances in biological environments can affect sensitivity and specificity. Notably, among the 30

articles using DENV-infected clinical samples, only 22 (73.3%) explicitly mentioned adherence to regulatory and ethical protocols, informed consent, or proper handling of biological samples. This highlights a gap in reporting critical information (Q3; Figure 2C and Supplemental File 4).

Most studies described the experimental protocol in detail (Q4, 84.7%) and demonstrated the robustness of their results by evaluating their impact compared to other options (Q5, 89.8%). However, inconsistencies in experimental design were noted, particularly in the assessment of biosensor performance. Differences in the methods used to determine sensitivity, specificity, and LoD made direct comparisons between studies challenging (Figure 2C and Supplemental File 4).

Additionally, many studies did not evaluate the potential limitations or challenges of the biosensor design in addressing the real needs of patients and the community (Q8, 66.3%; Figure 2C and Supplemental File 4).

Another critical issue was the potential bias from funding sources and undeclared conflicts of interest (Q9). A considerable number of studies ($n = 29$; 29.6%) did not disclose funding sources or commercial affiliations, which could have influenced data interpretation and reporting (Figure 2C and Supplemental File 4).

Addressing these gaps is crucial for ensuring the reliability and clinical applicability of biosensors for DENV detection. Future studies should prioritize methodological rigor by conducting validation with real patient samples, adhering to standardized diagnostic evaluation protocols, and ensuring transparency in funding disclosures and ethical compliance.

6 | Conclusion and Future Outlook

The recent surge in DENV cases represents a serious global health threat, underscoring the urgent need for effective control measures. Mosquito control and public health campaigns are vital in endemic regions, but early DENV diagnosis remains crucial for mitigating outbreaks. Traditional diagnostic methods, including antibody-based serological tests, cell culture, and PCR, each have limitations. Serological tests can cross-react with other flaviviruses, leading to misdiagnosis, while molecular tests are often complex, time-consuming, and require specialized personnel, making them less accessible in resource-limited settings. Thus, there is a pressing need for simple, cost-effective, and rapid diagnostic tests with high specificity for DENV.

6.1 | Summary of Key Findings and Current Status

Nanotechnology has greatly advanced optical biosensors for DENV detection, driven by innovations in biorecognition elements, transducers, and nanomaterial synthesis. These nanotechnology-based biosensors promise lower costs, faster detection, improved sensitivity, and the ability to work with smaller sample sizes. AuNPs and Au-derived nanolayers and nanostripes are commonly used due to their unique optical properties, enabling high sensitivity and specificity. They facilitate the detection of various DENV targets, including the E protein, NS1 protein, RNA, and anti-DENV antibodies. Hybrid nanomaterials, such as those combining AuNPs with graphene, QDs, or dendrimers, offer enhanced stability and improved Raman signals. These hybrids can achieve better sensitivity and lower LoD by leveraging the combined properties of their components. Nevertheless, balancing the cost of developing these hybrid materials with their performance is crucial.

SPR, colorimetric, and fluorescent assays can achieve excellent LoDs down to the femtomolar range. SPR is a widely used optical detection method due to its high sensitivity and specificity. SPR detects minute changes in refractive index, making it effective for precisely identifying small quantities of DENV. Unlike fluorescence or colorimetric methods, SPR does not require labeling, which simplifies the process and reduces costs. It also allows real-time monitoring of binding and dissociation kinetics. However, SPR systems can be expensive and complex, limiting their use in portable or miniaturized formats. Combining AuNPs with SPR biosensors enhances detection sensitivity due to the strong localized SPR of AuNPs, which amplifies the SPR signal. The morphology and size of NPs affect their optical properties, influencing the refractive index and interactions between NPs.

6.2 | Broader Opportunities and Challenges in Biosensor Development

Biosensors, with their versatile applications across biomedicine and food safety [292, 293], offer significant potential for improving disease diagnostics. Innovations in biosensor technologies focus on transduction mechanisms, such as optical, electrochemical, piezoelectric, and microfluidic/paper-based systems. These innovations aim to enhance DENV detection sensitivity and specificity while minimizing cross-reactivity. Moreover, biosensors provide several advantages over traditional methods, including the ability to differentiate between primary and secondary infections, thereby enabling early detection and monitoring of viral load and disease progression. Their high specificity is crucial for controlling outbreaks, even in vaccinated populations.

Despite their advantages, biosensors face several challenges that must be addressed for widespread clinical use [286, 294]. A major concern is their durability, as environmental factors like temperature, humidity, and light can degrade sensor components over time, affecting reliability, a nonnegotiable attribute for PoC devices. Moreover, ensuring the robustness of biological elements, particularly in fluctuating conditions, is crucial for long-term performance. Reproducibility is another issue, as variations in fabrication and materials can lead to inconsistent results. Standardizing manufacturing protocols, calibration methods, and quality control is essential for reliability. Complex biological matrices such as blood serum, plasma, and saliva can interfere with biosensor accuracy, posing a challenge for direct sample analysis in PoC settings. Cost and scalability also present barriers, as production and implementation expenses can limit accessibility, especially for widespread PoC adoption in DENV-endemic regions. Achieving cost-effective manufacturing while maintaining performance remains a challenge,

especially for large-scale deployment. Moreover, biosensor integration raises ethical concerns regarding privacy, data security, and informed consent; thus, balancing technological benefits with individual rights requires strong ethical frameworks. In summary, addressing these limitations is essential for advancing biosensor technology and ensuring its practical application in real-world settings.

6.3 | Future Directions in Nanotechnology-Enabled Optical Biosensors

Emerging diagnostic tools include engineered proteins, signaling aptamers, peptide arrays, and molecularly imprinted polymers. Advances in DNA nanotechnology [44, 295, 296], multiplex DNA microarrays [297], clustered regularly interspaced short palindromic repeat (CRISPR)-based assays [298, 299], and lab-on-a-chip microfluidic platforms [300, 301] also show promise (Figure 3). Crucially, lab-on-a-chip microfluidic platforms continue to advance, offering miniaturization, sample processing automation, and reduced reagent consumption, which are all essential for developing effective PoC testing [302–305]. The integration of such microdevices with portable optical readers or smartphone-based interfaces further enhances their PoC applicability by enabling quantitative analysis, user-friendly operation, and data connectivity for real-time surveillance and even potential for self-testing scenarios [306–311]. These developments aim to improve diagnostic sensitivity and accessibility, particularly in resource-limited settings where rapid and accurate DENV detection is paramount.

6.3.1 | Innovations in Nanomaterials and Green Synthesis

Green synthesis methods for nanomaterials have emerged as a promising approach to improve the sustainability of biosensor production while maintaining high efficiency in detection (Figure 3) [312–314]. These methods utilize biological resources such as plant extracts, microorganisms, and biopolymers as reducing and stabilizing agents, eliminating the need for hazardous chemicals. For instance, plant extracts rich in phenolic compounds, such as those from neem (*Azadirachta indica*) and turmeric (*Curcuma longa*), have been successfully used to synthesize AuNPs and AgNPs with enhanced stability and biocompatibility [315, 316]. Similarly, microbial-assisted synthesis using bacteria (*Bacillus subtilis*) and fungi (*Fusarium oxysporum*) has demonstrated the potential to produce nanomaterials with controlled size and shape, which is crucial for biosensor optimization [317, 318]. Additionally, natural polymers like chitosan and alginate serve as eco-friendly stabilizing agents, ensuring NP functionality while reducing cytotoxicity [319, 320]. These green synthesis approaches offer multiple advantages, including lower production costs, reduced environmental impact, and improved biocompatibility. Moreover, minimizing the use of toxic solvents and energy-intensive processes aligns with global efforts to develop sustainable nanotechnologies [321, 322]. However, challenges remain, such as a limited understanding of the interaction between green-synthesized nanomaterials and biorecognition molecules, the potential need for larger sample volumes with some methods, and ensuring the long-term sustainability and stability of the nanostructures themselves [312–314]. Future research should

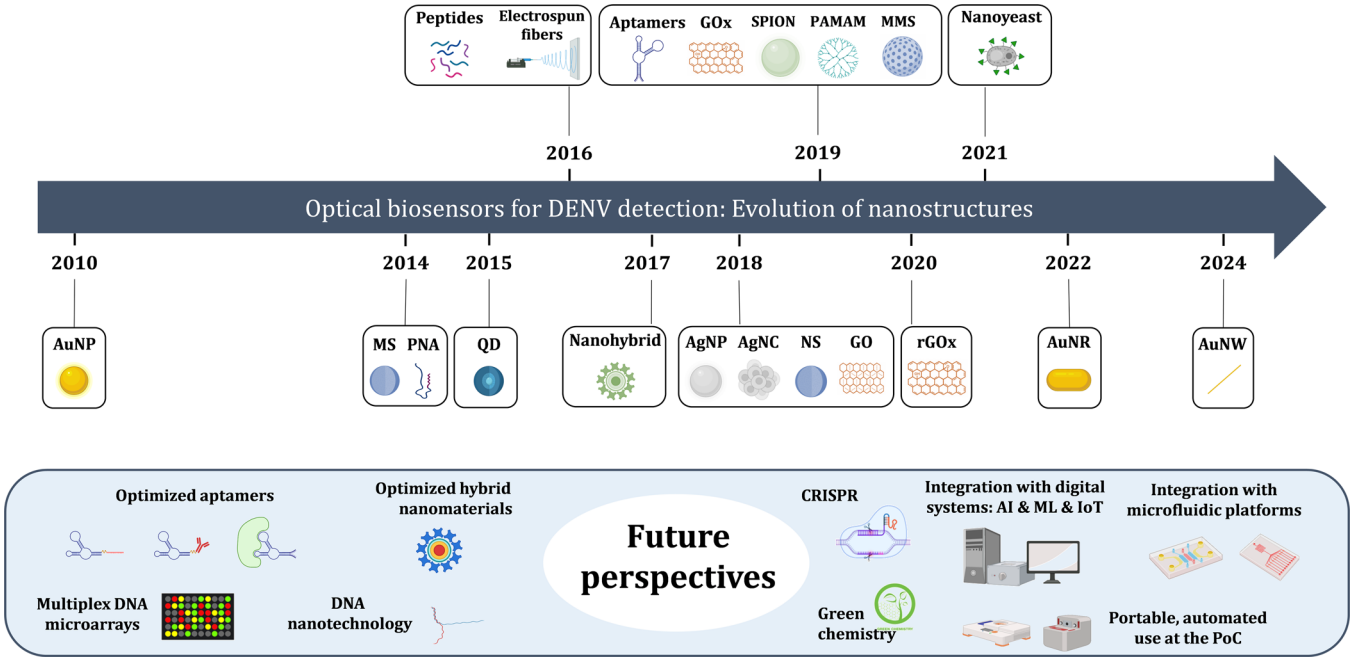

FIGURE 3 | Advances and prospects in nanotechnology-based optical biosensors for DENV detection. AgNC, silver nanocluster; AgNP, silver nanoparticle; AI, artificial intelligence; AuNP, gold nanoparticle; AuNR, gold nanorod; AuNW, gold nanowire; CRISPR, clustered regularly interspaced short palindromic repeats; DENV, dengue virus; DNA, deoxyribonucleic acid; GO, graphene; GOx, graphene oxide; IoT, Internet of Things; ML, machine learning; MMS, magnetic microsphere; MS, microsphere; NS, nanosphere; PAMAM, polyamidoamine; PNA, peptide nucleic acid; PoC, point of care; QD, quantum dot; rGOx, reduced graphene oxide; SPION, superparamagnetic iron oxide nanoparticle. [Color figure can be viewed at wileyonlinelibrary.com]

focus on integrating these green-synthesized nanomaterials into biosensing platforms to enhance their real-world applicability and facilitate regulatory approval.

6.3.2 | The Road Ahead for PoC Diagnostics

Optical biosensors offer great potential for rapid PoC DENV diagnosis, especially in resource-constrained settings. PoC testing is evolving with new technologies in materials, design, and detection, making diagnostics more accessible and personalized [323]. However, as highlighted by the studies included in this review, challenges remain in transforming laboratory advances into dependable PoC devices. Beyond external challenges such as unreliable power supplies, disruptions in the cold chain, and high transportation costs, many of the reviewed biosensor designs themselves do not yet adequately address the stringent requirements for PoC use, such as long-term stability, ease of use by nonspecialized personnel, affordability, and resilience to complex sample matrices without extensive preparation. Currently, PoC methods like lateral flow tests (e.g., Bio-Rad NS1 Ag Strip, PanBio-IgM/IgG, SD Dengue Duo) are available [324], but there is ongoing research to improve their analytical performance and sensitivity. Au and AgNPs, as discussed in this review, are key to enhancing PoC tests. Their unique, tunable optical properties enable sensitive detection methods such as colorimetry, SERS, and enhanced fluorescence, often used in microfluidic PoC devices [179]. Future research should focus on developing next-generation PoC devices that meet the ASSURED criteria [277]. Many of the promising technologies identified in this review require further development to meet these comprehensive criteria, particularly in terms of robustness, cost, and equipment-free operation, before their PoC potential can be fully realized. Moreover, future research should focus on identifying specific epitopes to reduce cross-reactivity and on developing rapid multiplex tests to detect all four DENV serotypes.

6.3.3 | Integrating Intelligent Systems

Computational analysis, artificial intelligence (AI), and machine learning (ML) offer exciting prospects for advancing biosensor technology (Figure 3) [325–329]. AI and ML are transforming healthcare by enhancing diagnostic accuracy, patient monitoring, and medical research [330–332]. In DENV detection, AI and ML have been applied to vector population modeling, outbreak prediction, and transmission analysis [333–337], but their potential extends to clinical diagnostics [338]. For instance, AI-driven automation of blood smear analysis facilitates rapid patient identification [339], and ML algorithms can distinguish DENV from Chikungunya virus early in presentation [340].

Crucially for nanotechnology-enabled optical biosensors, AI can refine complex signal processing (e.g., from SPR or SERS outputs), optimize sensor performance, and reduce false positives/negatives by integrating biosensor data with clinical and epidemiological information [287, 341]. This real-time AI-assisted approach can improve DENV diagnostic accuracy in diverse settings [91, 342].

The Internet of Medical Things (IoMT) is playing a growing role in healthcare automation [343, 344]. IoMT enables real-time data collection from connected diagnostic devices, remote monitoring, and rapid dissemination of results, as demonstrated by IoMT-enabled PCR systems for DENV [345, 346]. The integration of advanced nanomaterials with IoMT platforms holds promise for developing highly sensitive, scalable, and cost-effective real-time DENV diagnostics [344]. The use of AI with data from wearable sensors monitoring physiological parameters also shows potential for DENV risk stratification and improved patient care, complementing biosensor data [347]. Additionally, AI, including deep neural networks, is being used to authenticate unique tags created with plasmonic NPs, a concept that could potentially be adapted for secure and verifiable diagnostic test results [348].

In summary, integrating AI, ML, and IoMT with nanotechnology-based optical biosensors is poised to deliver highly sensitive, real-time, and cost-effective DENV diagnostics. Future research should focus on developing scalable, AI-integrated optical biosensors, particularly for resource-limited settings, to bridge the gap between laboratory innovations and real-world clinical applications.

7 | Strengths and Limitations of This Systematic Review

7.1 | Strengths

Our study followed a rigorous, standardized, pre-defined protocol to ensure consistency and minimize bias throughout the review process. We searched multiple international biomedical databases from 2010 to June 1, 2025, using relevant Medical Subject Headings (MeSH) terms and synonyms with no language restrictions. Citation chaining maximized study retrieval. Two independent researchers performed article selection, data extraction, and quality assessment. Disagreements were resolved through discussion or by a third reviewer, ensuring a rigorous review process. This methodology provides an updated understanding of nanotechnology-based optical biosensors for DENV detection, offering valuable insights and highlighting their potential and growing interest through an optimized study database.

7.2 | Limitations

Despite following PRISMA guidelines and employing standardized critical appraisal, several limitations prevent definitive conclusions. First, relevant studies might have been missed despite our comprehensive search strategy. Second, the included studies exhibited variable quality, scoring moderate-to-high on the CASP checklist but often lacking transparency regarding conflicts of interest and funding. Third, heterogeneity in study design, methods, and results, as well as the limited number of studies using human samples, restricts generalizability to clinical settings. Fourth, microfluidics-based technologies were excluded to focus on nanotechnology-based optical biosensors, thereby narrowing the scope. Lastly, we did not address the challenges of implementing these biosensors in clinical practice due to data limitations on implementation costs, intervention descriptions, and long-term outcomes.

Author Contributions

Marta Quero-Delgado: investigation, resources, data curation, writing – original draft. **Helena Codina:** investigation, resources, data curation, writing – review and editing. **Rafael Gómez:** investigation, writing – review and editing. Francisco José Terán: investigation, writing – review and editing. **M. A. Muñoz-Fernández:** investigation, writing – review and editing. **José Luis Jiménez:** investigation, writing – review and editing. **Salvador Resino:** methodology, funding acquisition, writing – review and editing. **Daniel Sepúlveda-Crespo:** conceptualization, methodology, formal analysis, data curation, writing – original draft, visualization, supervision, project administration, funding acquisition. **Isidoro Martínez:** conceptualization, methodology, writing – review and editing, visualization, supervision, project administration, funding acquisition. All authors have read and approved the final manuscript.

Acknowledgments

The authors acknowledge using AI tools such as ChatGPT (OpenAI) and Gemini (Google) to assist with language editing, grammar, and text flow. These tools were used under strict authorial control and supervision to refine the manuscript's presentation and did not contribute to the intellectual content. This study was supported by grants from Instituto de Salud Carlos III (ISCII; grant #PI23CIII/00018 to D.S.-C. and I.M., PI19CIII/00009 to I.M., PI20CIII/00004 to S.R., PI23/01137, PT23/00148 to M.A.M.F.). This study was also supported by the Consorcio Centro de Investigación Biomédica en Red (CIBER) (CB 2021), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea—NextGenerationEU: CIBERINFEC (CB21/13/00044 to S.R.) and CIBERBBN (CB22/01/00041 to M.A.M.F.). D.S.-C. is a "Miguel Servet" researcher from ISCIII (grant #CP23CIII/00004). Programa de Investigación de la Consejería de Sanidad de la Comunidad de Madrid to J.L.J. No funding bodies had any role in study design, data collection, analysis, publication decision, or manuscript preparation.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

1. S. Malik, O. Ahsan, H. Mumtaz, M. Tahir Khan, R. Sah, and Y. Waheed, "Tracing Down the Updates on Dengue Virus-Molecular Biology, Antivirals, and Vaccine Strategies," *Vaccines* 11 (2023): 1328, https://doi.org/10.3390/vaccines11081328.

2. P. R. Asish, S. Dasgupta, G. Rachel, B. S. Bagepally, and C. P. Girish Kumar, "Global Prevalence of Asymptomatic Dengue Infections—A Systematic Review and Meta-Analysis," *International Journal of Infectious Diseases* 134 (2023): 292–298, https://doi.org/10.1016/j.ijid.2023.07.010.

3. S. M. Stanley, H. K. Khera, S. Chandrasingh, C. E. George, and R. K. Mishra, "A Comprehensive Review of Dengue With a Focus on Emerging Solutions for Precision and Timely Detection," *International Journal of Biological Macromolecules* 254 (2023): 127613, https://doi.org/10.1016/j.ijbiomac.2023.127613.

4. J. Zeidler, L. Fernandes-Siqueira, G. Barbosa, and A. Da Poian, "Non-Canonical Roles of Dengue Virus Non-Structural Proteins," *Viruses* 9 (2017): 42, https://doi.org/10.3390/v9030042.

5. A. El Sahili and J. Lescar, "Dengue Virus Non-Structural Protein 5," *Viruses* 9 (2017): 91, https://doi.org/10.3390/v9040091.

6. X. Zhang, R. Jia, H. Shen, M. Wang, Z. Yin, and A. Cheng, "Structures and Functions of the Envelope Glycoprotein in Flavivirus Infections," *Viruses* 9 (2017): 338, https://doi.org/10.3390/v9110338.

7. J. G. H. Low, E. E. Ooi, and S. G. Vasudevan, "Current Status of Dengue Therapeutics Research and Development," *Journal of infectious diseases* 215 (2017): S96–S102, https://doi.org/10.1093/infdis/jiw423.

8. M. S. Mustafa, V. Rasotgi, S. Jain, and V. Gupta, "Discovery of Fifth Serotype of Dengue Virus (DENV-5): A New Public Health Dilemma in Dengue Control," *Medical Journal, Armed Forces India* 71 (2015): 67–70, https://doi.org/10.1016/j.mjafi.2014.09.011.

9. W. H. Wang, A. N. Urbina, M. R. Chang, et al., "Dengue Hemorrhagic Fever—A Systemic Literature Review of Current Perspectives on Pathogenesis, Prevention and Control," *Journal of Microbiology, Immunology and Infection* 53 (2020): 963–978, https://doi.org/10.1016/j.jmii.2020.03.007.

10. S. K. Roy and S. Bhattacharjee, "Dengue Virus: Epidemiology, Biology, and Disease Aetiology," *Canadian Journal of Microbiology* 67 (2021): 687–702, https://doi.org/10.1139/cjm-2020-0572.

11. M. Khurram, W. Qayyum, S. J. Hassan, S. Mumtaz, H. T. Bushra, and M. Umar, "Dengue Hemorrhagic Fever: Comparison of Patients With Primary and Secondary Infections," *Journal of Infection and Public Health* 7 (2014): 489–495, https://doi.org/10.1016/j.jiph.2014.05.005.

12. B. E. E. Martina, P. Koraka, and A. D. M. E. Osterhaus, "Dengue Virus Pathogenesis: An Integrated View," *Clinical Microbiology Reviews* 22 (2009): 564–581, https://doi.org/10.1128/CMR.00035-09.

13. M. G. Guzman, M. Alvarez, and S. B. Halstead, "Secondary Infection as a Risk Factor for Dengue Hemorrhagic Fever/Dengue Shock Syndrome: An Historical Perspective and Role of Antibody-Dependent Enhancement of Infection," *Archives of Virology* 158 (2013): 1445–1459, https://doi.org/10.1007/s00705-013-1645-3.

14. T. H. T. Nguyen, H. E. Clapham, K. L. Phung, et al., "Methods to Discriminate Primary From Secondary Dengue During Acute Symptomatic Infection," *BMC Infectious Diseases* 18 (2018): 375, https://doi.org/10.1186/s12879-018-3274-7.

15. M. Palanichamy Kala, A. L. St. John, and A. P. S. Rathore, "Dengue: Update on Clinically Relevant Therapeutic Strategies and Vaccines," *Current Treatment Options in Infectious Diseases* 15 (2023): 27–52, https://doi.org/10.1007/s40506-023-00263-w.

16. R. Kariyawasam, M. Lachman, S. Mansuri, S. Chakrabarti, and A. K. Boggild, "A Dengue Vaccine Whirlwind Update," *Therapeutic Advances in Infectious Disease* 10 (2023): 20499361231167274, https://doi.org/10.1177/20499361231167274.

17. T. Zohra, F. Saeed, A. Ikram, et al., "Nanomedicine as a Potential Novel Therapeutic Approach Against the Dengue Virus," *Nanomedicine* 18 (2023): 1567–1584, https://doi.org/10.2217/nnm-2022-0217.

18. D. Kellstein and L. Fernandes, "Symptomatic Treatment of Dengue: Should the NSAID Contraindication be Reconsidered?," *Postgraduate Medicine* 131 (2019): 109–116, https://doi.org/10.1080/00325481.2019.1561916.

19. M. Angelin, J. Sjölin, F. Kahn, et al., "Qdenga®—A Promising Dengue Fever Vaccine; Can It be Recommended to Non-Immune Travelers?," *Travel Medicine and Infectious Ddisease* 54 (2023): 102598, https://doi.org/10.1016/j.tmaid.2023.102598.

20. S. Sridhar, A. Luedtke, E. Langevin, et al., "Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy," *New England Journal of Medicine* 379 (2018): 327–340, https://doi.org/10.1056/NEJMoa1800820.

21. V. Naresh and N. Lee, "A Review on Biosensors and Recent Development of Nanostructured Materials-Enabled Biosensors," *Sensors* 21 (2021): 1109, https://doi.org/10.3390/s21041109.

22. S. Soni, V. Gill, A. Anusheel, et al., "Dengue, Chikungunya, and Zika: The Causes and Threats of Emerging and Re-Emerging Arboviral Diseases," *Cureus* 15 (2023): e41717, https://doi.org/10.7759/cureus.41717.

23. F. S. R. R. Teles, "Biosensors and Rapid Diagnostic Tests on the Frontier Between Analytical and Clinical Chemistry for Biomolecular Diagnosis of Dengue Disease: A Review," *Analytica Chimica Acta* 687 (2011): 28–42, https://doi.org/10.1016/j.aca.2010.12.011.

24. Y. T. Chen, Y. C. Lee, Y. H. Lai, et al., "Review of Integrated Optical Biosensors for Point-of-Care Applications," *Biosensors* 10 (2020): 209, https://doi.org/10.3390/bios10120209.

25. A. Sharma, R. K. Mishra, K. Y. Goud, et al., "Optical Biosensors for Diagnostics of Infectious Viral Disease: A Recent Update," *Diagnostics* 11 (2021): 2083, https://doi.org/10.3390/diagnostics11112083.

26. P. Damborský, J. Švitel, and J. Katrlík, "Optical Biosensors," *Essays in Biochemistry* 60 (2016): 91–100, https://doi.org/10.1042/EBC20150010.

27. A. V. Kabashin, V. G. Kravets, and A. N. Grigorenko, "Label-Free Optical Biosensing: Going Beyond the Limits," *Chemical Society Reviews* 52 (2023): 6554–6585, https://doi.org/10.1039/d3cs00155e.

28. A. Touhami, *Biosensors and Nanobiosensors: Design and Applications,"* Nanomedicine (One Central Press, 2014), 374.

29. P. Martinkova, A. Kostelnik, T. Valek, and M. Pohanka, "Main Streams in the Construction of Biosensors and Their Applications," *International Journal of Electrochemical Science* 12 (2017): 7386–7403, https://doi.org/10.20964/2017.08.02.

30. S. A. Abdullah, L. Najm, L. Ladouceur, et al., "Functional Nanomaterials for the Diagnosis of Alzheimer's Disease: Recent Progress and Future Perspectives," *Advanced Functional Materials* 33 (2023): 2302673, https://doi.org/10.1002/adfm.202302673.

31. M. Ma, Y. Zhang, K. Pu, and W. Tang, "Nanomaterial-Enabled Metabolic Reprogramming Strategies for Boosting Antitumor Immunity," *Chemical Society Reviews* 54 (2025): 653–714, https://doi.org/10.1039/d4cs00679h.

32. X. Sun, T. Tian, Y. Lian, and Z. Cui, "Current Advances in Viral Nanoparticles for Biomedicine," *ACS Nano* 18 (2024): 33827–33863, https://doi.org/10.1021/acsnano.4c13146.

33. G. Pasparakis, "Recent Developments in the Use of Gold and Silver Nanoparticles in Biomedicine," *WIREs Nanomedicine and Nanobiotechnology* 14 (2022): e1817, https://doi.org/10.1002/wnan.1817.

34. Y. Yang, Y. Liu, L. Song, et al., "Iron Oxide Nanoparticle-Based Nanocomposites in Biomedical Application," *Trends in Biotechnology* 41 (2023): 1471–1487, https://doi.org/10.1016/j.tibtech.2023.06.001.

35. P. Padmanabhan, A. Kumar, S. Kumar, R. K. Chaudhary, and B. Gulyás, "Nanoparticles in Practice for Molecular-Imaging Applications: An Overview," *Acta Biomaterialia* 41 (2016): 1–16, https://doi.org/10.1016/j.actbio.2016.06.003.

36. A. Gholami., M. Pourmadadi., H. Abdouss., et al., "Formulation of Double Microemulsion Based on pH-Responsive PEG/PVA/Zinc Oxide as a Potential Nano-Platform for Drug Delivery: Green Synthesis, and Physico-Chemical Characterization," *Journal of Molecular Liquids* 410 (2024): 125563, https://doi.org/10.1016/j.molliq.2024.125563.

37. R. Khoz, F. Yazdian, M. Pourmadadi, A. Rahdar, S. Fathi-karkan, and S. Pandey, "Current Trends in Silica Based Drug Delivery Systems," *European Journal of Medicinal Chemistry Reports* 12 (2024): 100206, https://doi.org/10.1016/j.ejmcr.2024.100206.

38. S. T. Jahan, S. M. A. Sadat, M. Walliser, and A. Haddadi, "Targeted Therapeutic Nanoparticles: An Immense Promise to Fight Against Cancer," *Journal of Drug Delivery* 2017 (2017): 9090325, https://doi.org/10.1155/2017/9090325.

39. S. Razzaq, I. Fatima, Z. Moafian, et al., "Nanomedicine Innovations In Colon and Rectal Cancer: Advances in Targeted Drug and Gene Delivery Systems," *Medical Oncology* 42 (2025): 113, https://doi.org/10.1007/s12032-025-02670-z.

40. F. R. Abbas Abad, M. Pourmadadi, M. Abdouss, A. Rahdar, S. Fathi-karkan, and S. Pandey, "Targeted Nanoparticle Delivery of Lapatinib for Cancer Therapy: Progress, Challenges, and Future Directions," *Journal of Drug Delivery Science and Technology* 108 (2025): 106902, https://doi.org/10.1016/j.jddst.2025.106902.

41. S. Sadr, A. Hajjafari, N. Lotfalizadeh, et al., "Phytosome-Based Nanotechnology for Enhanced Efficacy of Anticancer Phytocompounds: Challenges and Prospects," *Journal of Drug Delivery Science and Technology* 104 (2025): 106543, https://doi.org/10.1016/j.jddst.2024.106543.

42. L. Dykman, B. Khlebtsov, and N. Khlebtsov, "Drug Delivery Using Gold Nanoparticles," *Advanced Drug Delivery Reviews* 216 (2025): 115481, https://doi.org/10.1016/j.addr.2024.115481.

43. Y. Niu, G. Liu, M. Fu, et al., "Designing a Multifaceted Bio-Interface Nanofiber Tissue-Engineered Tubular Scaffold Graft to Promote Neo-Vascularization for Urethral Regeneration," *Journal of Materials Chemistry B* 8 (2020): 1748–1758, https://doi.org/10.1039/c9tb01915d.

44. L. Yuwen, S. Zhang, and J. Chao, "Recent Advances in DNA Nanotechnology-Enabled Biosensors for Virus Detection," *Biosensors* 13 (2023): 822, https://doi.org/10.3390/bios13080822.

45. I. Ahmadi, M. Pourmadadi, F. Yazdian, H. Rashedi, A. Rahdar, and S. Pandey, "Detection of Prostate Specific Antigen Using a Magnetic Sulfonated Reduced Graphene Oxide/Gold Nanoparticle Aptasensor," *Next Nanotechnology* 2 (2023): 100017, https://doi.org/10.1016/j.nxnano.2023.100017.

46. A. Esmaeilian, F. Yazdian, A. Saberi, et al., "Innovations in Self-Powered Glucose Biosensors: From Energy Harvesting to Continuous, Non-Invasive Monitoring," *Inorganic Chemistry Communications* 174 (2025): 114076, https://doi.org/10.1016/j.inoche.2025.114076.

47. P. Yari, S. Liang, V. K. Chugh, et al., "Nanomaterial-Based Biosensors for SARS-CoV-2 and Future Epidemics," *Analytical Chemistry* 95 (2023): 15419–15449, https://doi.org/10.1021/acs.analchem.3c01522.

48. R. Fu and Y. Xianyu, "Gold Nanomaterials-Implemented CRISPR-Cas Systems for Biosensing," *Small* 19 (2023): e2300057, https://doi.org/10.1002/smll.202300057.

49. M. Kim, S. Hong, R. Khan, J. J. Park, J. B. In, and S. H. Ko, "Recent Advances in Nanomaterial-Based Biosignal Sensors," *Small* 21 (2025): e2405301, https://doi.org/10.1002/smll.202405301.

50. B. Brasiunas, A. Popov, V. Lisyte, A. Kausaite-Minkstimiene, and A. Ramanaviciene, "ZnO Nanostructures: A Promising Frontier in Immunosensor Development," *Biosensors and Bioelectronics* 246 (2024): 115848, https://doi.org/10.1016/j.bios.2023.115848.

51. D. Quesada-González and A. Merkoçi, "Quantum Dots for Biosensing: Classification and Applications," *Biosensors and Bioelectronics* 273 (2025): 117180, https://doi.org/10.1016/j.bios.2025.117180.

52. M. Ramesh, R. Janani, C. Deepa, and L. Rajeshkumar, "Nanotechnology-Enabled Biosensors: A Review of Fundamentals, Design Principles, Materials, and Applications," *Biosensors* 13 (2022): 40, https://doi.org/10.3390/bios13010040.

53. S. Malik, K. Muhammad, and Y. Waheed, "Emerging Applications of Nanotechnology in Healthcare and Medicine," *Molecules* 28 (2023): 6624, https://doi.org/10.3390/molecules28186624.

54. Y. Fu, T. Liu, H. Wang, et al., "Applications of Nanomaterial Technology in Biosensing," *Journal of Science: Advanced Materials and Devices* 9 (2024): 100694, https://doi.org/10.1016/j.jsamd.2024.100694.

55. F. García-Álvarez and M. Martínez-García, "Click Reaction in the Synthesis of Dendrimer Drug-Delivery Systems," *Current Medicinal Chemistry* 29 (2022): 3445–3470, https://doi.org/10.2174/0929867328666211027124724.

56. Y. Gao, J. Wang, X. Mu, et al., "Carbon Quantum Dots in Spectrofluorimetric Analysis: A Comprehensive Review of Synthesis, Mechanisms and Multifunctional Applications," *Talanta* 293 (2025): 128066, https://doi.org/10.1016/j.talanta.2025.128066.

57. S. Zhang, N. Kong, Z. Wang, et al., "Nanochemistry of Gold: From Surface Engineering to Dental Healthcare Applications," *Chemical Society Reviews* 53 (2024): 3656–3686, https://doi.org/10.1039/d3cs00894k.

58. S. Kumar, S. M. Z. Mehdi, and Y. Seo, "1D MXenes: Synthesis, Properties, and Applications," *Small* 20 (2024): e2405576, https://doi.org/10.1002/smll.202405576.

59. C. Li, X. Jiang, and N. Yang, "Synthesis, Surface Chemistry, and Applications of Non-Zero-Dimensional Diamond Nanostructures," *Small* 20 (2024): e2400798, https://doi.org/10.1002/smll.202400798.

60. B. Rezaei, P. Yari, S. M. Sanders, et al., "Magnetic Nanoparticles: A Review on Synthesis, Characterization, Functionalization, and Biomedical Applications," *Small* 20 (2024): e2304848, https://doi.org/10.1002/smll.202304848.

61. H. Duman, E. Akdaşçi, F. Eker, M. Bechelany, and S. Karav, "Gold Nanoparticles: Multifunctional Properties, Synthesis, and Future Prospects," *Nanomaterials* 14 (2024): 1805, https://doi.org/10.3390/nano14221805.

62. A. Sati, T. N. Ranade, S. N. Mali, et al., "Silver Nanoparticles (AgNPs) as Potential Antiviral Agents: Synthesis, Biophysical Properties, Safety, Challenges and Future Directions—Update Review," *Molecules* 30 (2025): 2004, https://doi.org/10.3390/molecules30092004.

63. M. A. Kabir, H. Zilouchian, M. A. Younas, and W. Asghar, "Dengue Detection: Advances in Diagnostic Tools From Conventional Technology to Point of Care," *Biosensors* 11 (2021): 206, https://doi.org/10.3390/bios11070206.

64. S. S. Hegde and B. R. Bhat, "Dengue Detection: Advances and Challenges in Diagnostic Technology," *Biosensors and Bioelectronics: X* 10 (2022): 100100, https://doi.org/10.1016/j.biosx.2021.100100.

65. R. Eivazzadeh-Keihan, P. Pashazadeh-Panahi, T. Mahmoudi, et al., "Dengue Virus: A Review on Advances in Detection and Trends - From Conventional Methods to Novel Biosensors," *Microchimica Acta* 186 (2019): 329, https://doi.org/10.1007/s00604-019-3420-y.

66. M. R. Hasan, P. Sharma, S. Khan, et al., "Dengue-Virosensor: Advancement of Dengue Virus-Based Biosensors," *Sensors and Diagnostics* 4 (2024): 7–23, https://doi.org/10.1039/d4sd00262h.

67. S. N. Rajaei, M. Darvish, A. Zare, et al., "Advances in Nanobiosensors for Rapid and Sensitive Detection of Dengue Virus Biomarkers by Using Clinical Laboratory," *Journal of Clinical Laboratory Analysis* 39 (2025): e70012, https://doi.org/10.1002/jcla.70012.

68. M. B. Khan, Z. S. Yang, C. Y. Lin, et al., "Dengue Overview: An Updated Systemic Review," *Journal of Infection and Public Health* 16 (2023): 1625–1642, https://doi.org/10.1016/j.jiph.2023.08.001.

69. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *BMJ* 372 (2021): n71, https://doi.org/10.1136/bmj.n71.

70. E. D. Foster and A. Deardorff, "Open Science Framework (OSF)," *Journal of the Medical Library Association* 105 (2017): 203–206, https://doi.org/10.5195/jmla.2017.88.

71. D. Pieper and T. Rombey, "Where to Prospectively Register a Systematic Review," *Systematic Reviews* 11 (2022): 8, https://doi.org/10.1186/s13643-021-01877-1.

72. M. B. Eriksen and T. F. Frandsen, "The Impact of Patient, Intervention, Comparison, Outcome (PICO) as a Search Strategy Tool on Literature Search Quality: A Systematic Review," *Journal of the Medical Library Association* 106 (2018): 420–431, https://doi.org/10.5195/jmla.2018.345.

73. J. R. Landis and G. G. Koch, "The Measurement of Observer Agreement for Categorical Data," *Biometrics* 33 (1977): 159–174.

74. K. Kolaski, L. R. Logan, and J. P. A. Ioannidis, "Guidance to Best Tools and Practices for Systematic Reviews," *JBJS Reviews* 11 (2023): e23.00077, https://doi.org/10.2106/JBJS.RVW.23.00077.

75. C. O'dwyer, L. Tarzia, S. Fernbacher, and K. Hegarty, "Health Professionals' Experiences of Providing Trauma-Informed Care in Acute Psychiatric Inpatient Settings: A Scoping Review," *Trauma, Violence & Abuse* 22 (2021): 1057–1067, https://doi.org/10.1177/1524838020903064.

76. W. P. Costa, M. S. V. Fernandes, A. R. Memon, P. R. E. S. Noll, M. M. Sousa, and M. Noll, "Factors Influencing the Work of Researchers in Scientific Initiation: A Systematic Review Protocol," *PLoS One* 19 (2024): e0297186, https://doi.org/10.1371/journal.pone.0297186.

77. P. E. Shrout and J. L. Fleiss, "Intraclass Correlations: Uses in Assessing Rater Reliability," *Psychological Bulletin* 86 (1979): 420–428, https://doi.org/10.1037//0033-2909.86.2.420.

78. T. K. Koo and M. Y. Li, "A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research," *Journal of Chiropractic Medicine* 15 (2016): 155–163, https://doi.org/10.1016/j.jcm.2016.02.012.

79. S. K. Gahlaut, A. Pathak, B. D. Gupta, and J. P. Singh, "Portable Fiber-Optic SPR Platform for the Detection of NS1-Antigen for Dengue Diagnosis," *Biosensors and Bioelectronics* 196 (2022): 113720, https://doi.org/10.1016/j.bios.2021.113720.

80. F. C. C. L. Loureiro, H. Neff, E. U. K. Melcher, et al., "Simplified Immunoassay for Rapid Dengue Serotype Diagnosis, Revealing Insensitivity to Non-Specific Binding Interference," *Sensing and Bio-Sensing Research* 13 (2017): 96–103, https://doi.org/10.1016/j.sbsr.2016.10.002.

81. P. Jahanshahi, E. Zalnezhad, S. D. Sekaran, and F. R. M. Adikan, "Rapid Immunoglobulin M-Based Dengue Diagnostic Test Using Surface Plasmon Resonance Biosensor," *Scientific Reports* 4 (2014): 3851, https://doi.org/10.1038/srep03851.

82. S. Kumbhat, K. Sharma, R. Gehlot, A. Solanki, and V. Joshi, "Surface Plasmon Resonance Based Immunosensor for Serological Diagnosis of Dengue Virus Infection," *Journal of Pharmaceutical and Biomedical Analysis* 52 (2010): 255–259, https://doi.org/10.1016/j.jpba.2010.01.001.

83. N. A. S. Omar, Y. W. Fen, J. Abdullah, C. E. N. C. E. Chik, and M. A. Mahdi, "Development of an Optical Sensor Based on Surface Plasmon Resonance Phenomenon for Diagnosis of Dengue Virus E-Protein," *Sensing and Bio-Sensing Research* 20 (2018): 16–21, https://doi.org/10.1016/j.sbsr.2018.06.001.

84. W. R. Wong, O. Krupin, S. D. Sekaran, F. R. Mahamd Adikan, and P. Berini, "Serological Diagnosis of Dengue Infection in Blood Plasma Using Long-Range Surface Plasmon Waveguides," *Analytical Chemistry* 86 (2014): 1735–1743, https://doi.org/10.1021/ac403539k.

85. C. R. Basso, C. C. Tozato, B. P. Crulhas, G. R. Castro, J. P. A. Junior, and V. A. Pedrosa, "An Easy Way to Detect Dengue Virus Using Nanoparticle-Antibody Conjugates," *Virology* 513 (2018): 85–90, https://doi.org/10.1016/j.virol.2017.10.001.

86. A. R. Camara, P. M. P. Gouvêa, A. C. M. S. Dias, et al., "Dengue Immunoassay With an LSPR Fiber Optic Sensor," *Optics Express* 21 (2013): 27023–27031, https://doi.org/10.1364/OE.21.027023.

87. A. F. Versiani, E. M. N. Martins, L. M. Andrade, et al., "Nanosensors Based on LSPR Are Able to Serologically Differentiate Dengue From Zika Infections," *Scientific Reports* 10 (2020): 11302, https://doi.org/10.1038/s41598-020-68357-9.

88. S. Farooq, F. Wali, D. M. Zezell, R. E. de Araujo, and D. Rativa, "Optimizing and Quantifying Gold Nanospheres Based on LSPR Label-Free Biosensor for Dengue Diagnosis," *Polymers* 14 (2022): 1592, https://doi.org/10.3390/polym14081592.

89. H. Z. Mahmood, A. Jilani, S. Farooq, et al., "Plasmon-Based Label-Free Biosensor Using Gold Nanosphere for Dengue Detection," *Crystals* 11 (2021): 1340, https://doi.org/10.3390/cryst11111340.

90. L. Zhang, R. Zhang, L. Cui, et al., "Application of a Graphene-Oxide-Modified Surface Plasmon Resonance Biosensor in Dengue E-Protein Detection," *Applied Physics A* 128 (2022): 1019, https://doi.org/10.1007/s00339-022-06085-9.

91. N. A. S. Omar, Y. W. Fen, J. Abdullah, et al., "Sensitive Detection of Dengue Virus Type 2 E-Proteins Signals Using Self-Assembled Monolayers/Reduced Graphene Oxide-PAMAM Dendrimer Thin Film-SPR Optical Sensor," *Scientific Reports* 10 (2020): 2374, https://doi.org/10.1038/s41598-020-59388-3.

92. M. T. Torres do Couto, A. Galdino da Silva Júnior, K. Y. Pereira Dos Santos Avelino, et al., "Development of Optical and Electrochemical Immunodevices for Dengue Virus Detection," *Analytical Methods* 16 (2024): 3539–3550, https://doi.org/10.1039/d4ay00514g.

93. A. D. Chowdhury, K. Takemura, I. M. Khorish, et al., "The Detection and Identification of Dengue Virus Serotypes With Quantum Dot and AuNP Regulated Localized Surface Plasmon Resonance," *Nanoscale Advances* 2 (2020): 699–709, https://doi.org/10.1039/c9na00763f.

94. N. Omar, Y. Fen, S. Saleviter, et al., "Development of a Graphene-Based Surface Plasmon Resonance Optical Sensor Chip for Potential Biomedical Application," *Materials* 12 (2019): 1928, https://doi.org/10.3390/ma12121928.

95. N. A. S. Omar, Y. W. Fen, J. Abdullah, M. H. M. Zaid, W. M. E. M. M. Daniyal, and M. A. Mahdi, "Sensitive Surface Plasmon Resonance Performance of Cadmium Sulfide Quantum Dots-Amine Functionalized Graphene Oxide Based Thin Film Towards Dengue Virus E-Protein," *Optics & Laser Technology* 114 (2019): 204–208, https://doi.org/10.1016/j.optlastec.2019.01.038.

96. N. A. S. Omar, Y. W. Fen, S. Saleviter, et al., "Experimental Evaluation on Surface Plasmon Resonance Sensor Performance Based on Sensitive Hyperbranched Polymer Nanocomposite Thin Films," *Sensors and Actuators, A: Physical* 303 (2020): 111830, https://doi.org/10.1016/j.sna.2020.111830.

97. N. A. S. Omar, Y. W. Fen, J. Abdullah, N. A. A. Anas, N. S. M. Ramdzan, and M. A. Mahdi, "Optical and Structural Properties of Cadmium Sulphide Quantum Dots Based Thin Films as Potential Sensing Material for Dengue Virus E-Protein," *Results in Physics* 11 (2018): 734–739, https://doi.org/10.1016/j.rinp.2018.10.032.

98. V. Yesudasu, R. Srivastava, S. Pal, A. Verma, and Y. K. Prajapati, "Performance Enhancement of SPR Sensor for Dengue Virus Detection: Influence of Aluminum Nitride and 2D Materials," *Plasmonics* 20 (2024): 3973–3986, https://doi.org/10.1007/s11468-024-02574-0.

99. B. Karki, N. H. Salah, G. Srivastava, A. Muduli, and R. B. Yadav, "A Simulation Study for Dengue Virus Detection Using Surface Plasmon Resonance Sensor Heterostructure of Silver, Barium Titanate, and Cerium Oxide," *Plasmonics* 18 (2023): 2031–2040, https://doi.org/10.1007/s11468-023-01907-9.

100. S. K. Saini and S. K. Awasthi, "Surface Plasmon Resonance-Based Hybrid Nanostructured Biosensor Composed of Ag–BP–CeO_2 Material Layers: A Theoretical Analysis," *Sensing and Imaging* 26 (2025): 82, https://doi.org/10.1007/s11220-024-00523-z.

101. M. G. Daher, S. A. Taya, O. S. Faragallah, and A. Armghan, "Designing of High-Sensitivity Optical Surface Plasmon Resonance Sensor (OSPRS) for Fast and Accurate Diagnosis of Dengue Virus (DeVs)," *Plasmonics* 20 (2024): 3887–3895, https://doi.org/10.1007/s11468-024-02593-x.

102. R. Jena, P. Dhar, A. Panda, F. Wu, and M. G. Daher, "An Investigation on Hybrid AlN-Graphene Surface Plasmon Resonance Sensor for Refractive Index-Based Pathogen Detection," *Microchimica Acta* 192 (2025): 351, https://doi.org/10.1007/s00604-025-07226-6.

103. S. A. Rafi, T. P. Mondal, R. R. Mahmud, et al., "Innovative TiO_2/Ag/TiO_2 Sandwiched SPR Sensor With WSe_2 Layer for Efficient Dengue Virus Detection via TMM and FEM," *Plasmonics* 20 (2025): 5345–5361, https://doi.org/10.1007/s11468-024-02730-6.

104. C. Basak, M. K. Hosain, M. S. Islam, and A. Z. Kouzani, "Design and Modeling of an Angular Interrogation Based Surface Plasmon Resonance Biosensor for Dengue Virus Detection," *Optical and Quantum Electronics* 55 (2023): 438, https://doi.org/10.1007/s11082-023-04708-w.

105. A. Banerjee and J. Thangaraj, "SPR-Based Refractive Index Sensor Design With Grated Au-ZnS for Dengue Detection Using Machine Learning," *Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy* 339 (2025): 126276, https://doi.org/10.1016/j.saa.2025.126276.

106. G. L. Machado, F. M. F. Teixeira, G. S. C. Ferreira, et al., "Computational Guided Method Applied to LSPR-Based Biosensor for Specific Detection of the Four-Serotypes of Dengue Virus in Seropositive Patients," *Particle & Particle Systems Characterization* 39 (2022): 2100157, https://doi.org/10.1002/ppsc.202100157.

107. S. Senapati and M. Mishra, "Boosting the Sensitivity of Cu-Based SPR Dengue Sensor Using Cu/Compound Semiconductor/$BaTiO_3$ Configuration for Effective Early-Stage Dengue Detection," *Plasmonics* (2025), https://doi.org/10.1007/s11468-025-02790-2.

108. P. Kumar, R. Kumar, M. K. Singh, and B. Ahmed, "Detection of Plasma, Platelets, Hemoglobin in Blood Sample of Dengue Malaria Based on Surface Plasmon Resonance Biosensor Using Black Phosphorus: A Numerical Analysis," *Plasmonics* 19 (2024): 1779–1790, https://doi.org/10.1007/s11468-023-02113-3.

109. V. Kumar, R. Kumar, S. Pal, and Y. K. Prajapati, "Development of Surface Plasmon Resonance Sensor Utilizing Gase and WS2 for Ultra-Sensitive Early Detection of Dengue Virus," *Optik* 313 (2024): 171975, https://doi.org/10.1016/j.ijleo.2024.171975.

110. M. Uwais and V. Rastogi, "Cu-Grating and Graphene-Assisted SPR-Based Refractive Index Sensor," *Plasmonics* (2025), https://doi.org/10.1007/s11468-025-02992-8.

111. N. P. Singh, A. C. Mishra, S. Yadav, et al., "Numerical Analysis of Silicon Nitride and Perovskite Nanomaterial Assisted SPR Biosensor for Dengue Cell Detection," *Journal of Optics* (2024), https://doi.org/10.1007/s12596-024-02224-y.

112. A. Panda and P. D. Pukhrambam, "Design and Modelling of Reconfigurable Surface Plasmon Resonance Refractive Index Sensor Employing Graphene and Sb_2S3 for Detection of Dengue Virus," *Physica B: Condensed Matter* 638 (2022): 413965, https://doi.org/10.1016/j.physb.2022.413965.

113. P. Upender and A. Kumar, "Numerical Investigation of a High-Performance Mxene and Graphene-Based Metamaterial Absorber for Terahertz Biosensing," *Results in Physics* 70 (2025): 108185, https://doi.org/10.1016/j.rinp.2025.108185.

114. A. H. M. Almawgani, P. Sarkar, A. Pal, et al., "Titanium Disilicide, Black Phosphorus-Based Surface Plasmon Resonance Sensor for Dengue Detection," *Plasmonics* 18 (2023): 1223–1232, https://doi.org/10.1007/s11468-023-01856-3.

115. S. K. Chan, Y. S. Choong, D. Perera, and T. S. Lim, "Dengue Serotyping With a Label-Free DNA Sensor," *Analytical Methods* 10 (2018): 214–222, https://doi.org/10.1039/C7AY02131C.

116. J. Mok, J. Jeon, J. Jo, E. Kim, and C. Ban, "Novel One-Shot Fluorescent Aptasensor for Dengue Fever Diagnosis Using NS1-induced Structural Change of G-Quadruplex Aptamer," *Sensors and Actuators B: Chemical* 343 (2021): 130077, https://doi.org/10.1016/j.snb.2021.130077.

117. P. S. Kwon, S. Ren, S. J. Kwon, et al., "Designer DNA Architecture Offers Precise and Multivalent Spatial Pattern-Recognition for Viral Sensing and Inhibition," *Nature Chemistry* 12 (2020): 26–35, https://doi.org/10.1038/s41557-019-0369-8.

118. S. J. Fletcher, L. W. Phillips, A. S. Milligan, and S. J. Rodda, "Toward Specific Detection of Dengue Virus Serotypes Using a Novel

Modular Biosensor," *Biosensors and Bioelectronics* 26 (2010): 1696–1700, https://doi.org/10.1016/j.bios.2010.07.046.

119. J.-S. Lee, J. Kim, H. Shin, and D.-H. Min, "Graphene Oxide-Based Molecular Diagnostic Biosensor for Simultaneous Detection of Zika and Dengue Viruses," *2D Materials* 7 (2020): 044001, https://doi.org/10.1088/2053-1583/ab9a64.

120. P. Kanagavalli and M. Veerapandian, "Opto-Electrochemical Functionality of Ru(II)-Reinforced Graphene Oxide Nanosheets for Immunosensing of Dengue Virus Non-Structural 1 Protein," *Biosensors and Bioelectronics* 150 (2020): 111878, https://doi.org/10.1016/j.bios.2019.111878.

121. L. D. Hein, I. N. Castillo, F. A. Medina, et al., "Multiplex Sample-Sparing Assay for Detecting Type-Specific Antibodies to Zika and Dengue Viruses: An Assay Development and Validation Study," *Lancet Microbe* 6 (2025): 100951, https://doi.org/10.1016/j.lanmic.2024.07.014.

122. G. P. Anderson, J. L. Liu, L. C. Shriver-Lake, et al., "Oriented Immobilization of Single-Domain Antibodies Using SpyTag/Spycatcher Yields Improved Limits of Detection," *Analytical Chemistry* 91 (2019): 9424–9429, https://doi.org/10.1021/acs.analchem.9b02096.

123. J. Tyson, W. Y. Tsai, J. J. Tsai, et al., "A High-Throughput and Multiplex Microsphere Immunoassay Based on Non-Structural Protein 1 Can Discriminate Three Flavivirus Infections," *PLoS Neglected Tropical Diseases* 13 (2019): e0007649, https://doi.org/10.1371/journal.pntd.0007649.

124. S. T. Gaylord, S. Abdul-Aziz, and D. R. Walt, "Single-Molecule Arrays for Ultrasensitive Detection of Host Immune Response to Dengue Virus Infection," *Journal of Clinical Microbiology* 53 (2015): 1722–1724, https://doi.org/10.1128/JCM.03487-14.

125. S. Hosseini, F. Ibrahim, I. Djordjevic, et al., "Synthesis and Characterization of Methacrylic Microspheres for Biomolecular Recognition: Ultrasensitive Biosensor for Dengue Virus Detection," *European Polymer Journal* 60 (2014): 14–21, https://doi.org/10.1016/j.eurpolymj.2014.08.010.

126. G. A. Ortega, J. C. Zuaznabar-Gardona, O. Morales-Tarré, and E. Reguera, "Immobilization of Dengue Specific IgM Antibodies on Magnetite Nanoparticles by Using Facile Conjugation Strategies," *RSC Advances* 6 (2016): 98457–98465, https://doi.org/10.1039/C6RA23260D.

127. A. H. Mahmud, M. Z. B. Abdul Halim, M. T. Mohd Ali, and A. M. M. Jani, "Enhancing Dengue DNA Biorecognition Through Surface Modification of Nanostructured Porous Surfaces With Hybridization Fluorescent Probes," *Emergent Materials* 8 (2025): 561–575, https://doi.org/10.1007/s42247-024-00880-1.

128. P. Melpignano, E. Daniso, and N. Vidergar, "Multiparametric Oled-Based Biosensor for Rapid Dengue Serotype Recognition With a New Point-of-Care Serological Test," *Informacije MIDEM* 46 (2016): 250–256, no DOI available.

129. E. M. Linares, C. S. Pannuti, L. T. Kubota, and S. Thalhammer, "Immunospot Assay Based on Fluorescent Nanoparticles for Dengue Fever Detection," *Biosensors and Bioelectronics* 41 (2013): 180–185, https://doi.org/10.1016/j.bios.2012.08.005.

130. L. Tran and S. Park, "Highly Sensitive Detection of Dengue Biomarker Using Streptavidin-Conjugated Quantum Dots," *Scientific Reports* 11 (2021): 15196, https://doi.org/10.1038/s41598-021-94172-x.

131. A. Ranzoni, A. den Hamer, T. Karoli, J. Buechler, and M. A. Cooper, "Improved Immunoassay Sensitivity in Serum as a Result of Polymer-Entrapped Quantum Dots: 'Papaya Particles'," *Analytical Chemistry* 87 (2015): 6150–6157, https://doi.org/10.1021/acs.analchem.5b00762.

132. W. Shen and Z. Gao, "Quantum Dots and Duplex-Specific Nuclease Enabled Ultrasensitive Detection and Serotyping of Dengue Viruses in One Step in a Single Tube," *Biosensors and Bioelectronics* 65 (2015): 327–332, https://doi.org/10.1016/j.bios.2014.10.060.

133. O. Adegoke, K. I. Gray, K. O. Adeniyi, O. J. Achadu, and S. Khene, "Multichannel Nanosensor for Rapid Virus Discrimination Using Fluorescence Sensing Pattern Array of Quantum Dot-Gold Nanoparticle Nano-Assemblies," *Colloids and Surfaces, A: Physicochemical and Engineering Aspects* 711 (2025): 136386, https://doi.org/10.1016/j.colsurfa.2025.136386.

134. Y. N. Monday, J. Abdullah, N. A. Yusof, S. Abdul Rashid, R. H. Shueb, and H. Sidek, "Carbon Quantum Dots Coupled Au Nanoparticle as Fluorescence-Based DNA Biosensors for Dengue Virus Detection," *Sains Malaysiana* 52 (2023): 3307–3323, https://doi.org/10.17576/jsm-2023-5211-21.

135. O. Adegoke and E. Y. Park, "Bright Luminescent Optically Engineered Core/Alloyed Shell Quantum Dots: An Ultrasensitive Signal Transducer for Dengue Virus RNA via Localized Surface Plasmon Resonance-Induced Hairpin Hybridization," *Journal of Materials Chemistry B* 5 (2017): 3047–3058, https://doi.org/10.1039/c7tb00388a.

136. A. Dutta Chowdhury, A. B. Ganganboina, F. Nasrin, et al., "Femtomolar Detection of Dengue Virus DNA With Serotype Identification Ability," *Analytical Chemistry* 90 (2018): 12464–12474, https://doi.org/10.1021/acs.analchem.8b01802.

137. O. Zavoiura, U. Resch-Genger, and O. Seitz, "Quantum Dot-PNA Conjugates for Target-Catalyzed RNA Detection," *Bioconjugate Chemistry* 29 (2018): 1690–1702, https://doi.org/10.1021/acs.bioconjchem.8b00157.

138. K. Sitthisuwannakul, R. Sukthai, Z. Zhu, et al., "Urinary Dengue NS1 Detection on Au-Decorated ZnO Nanowire Platform," *Biosensors and Bioelectronics* 254 (2024): 116218, https://doi.org/10.1016/j.bios.2024.116218.

139. S. Vinayagam, P. Rajaiah, A. Mukherjee, and C. Natarajan, "DNA-Triangular Silver Nanoparticles Nanoprobe for the Detection of Dengue Virus Distinguishing Serotype," *Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy* 202 (2018): 346–351, https://doi.org/10.1016/j.saa.2018.05.047.

140. M. S. C. Flores, E. C. Alocilja, D. M. Amalin, et al., "DNA-Based Nanobiosensor for the Colorimetric Detection of Dengue Virus Serotype 2 Synthetic Target Oligonucleotide," *Biosensors* 15 (2025): 71, https://doi.org/10.3390/bios15020071.

141. V. T. Cam Duyen, V. Van Toi, T. Van Hoi, and P. L. Truong, "A Novel Colorimetric Biosensor for Rapid Detection of Dengue Virus Upon Acid-Induced Aggregation of Colloidal Gold," *Analytical Methods* 15 (2023): 3991–3999, https://doi.org/10.1039/d3ay00756a.

142. S. Vinayagam, P. Rajaiah, A. Mukerjee, and C. Natarajan, "Nucleic Acid Detection Strategy Using Gold Nanoprobe of Two Diverse Origin," *IET Nanobiotechnology* 13 (2019): 928–932, https://doi.org/10.1049/iet-nbt.2018.5332.

143. I. M. Khoris, F. Nasrin, A. D. Chowdhury, and E. Y. Park, "Advancement of Dengue Virus NS1 Protein Detection by 3D-Nanoassembly Complex Gold Nanoparticles Utilizing Competitive Sandwich Aptamer on Disposable Electrode," *Analytica Chimica Acta* 1207 (2022): 339817, https://doi.org/10.1016/j.aca.2022.339817.

144. C. R. Basso, B. P. Crulhas, M. Magro, F. Vianello, and V. A. Pedrosa, "A New Immunoassay of Hybrid Nanomater Conjugated to Aptamers for the Detection of Dengue Virus," *Talanta* 197 (2019): 482–490, https://doi.org/10.1016/j.talanta.2019.01.058.

145. S. Abdul Rahman, R. Saadun, N. E. Azmi, et al., "Label-Free Dengue Detection Utilizing PNA/DNA Hybridization Based on the Aggregation Process of Unmodified Gold Nanoparticles," *Journal of Nanomaterials* 2014 (2014): 839286, https://doi.org/10.1155/2014/839286.

146. U. Dasgupta, M. Ghosh, R. Gangopadhyay, et al., "Synergistic Role of the AuAg-Fe(3)O(4) Nanoenzyme for Ultrasensitive Immunoassay of Dengue Virus," *ACS Omega* 9 (2024): 40051–40060, https://doi.org/10.1021/acsomega.4c05937.

147. S. Hosseini, P. Azari, B. Cardenas-Benitez, et al., "A LEGO Inspired Fiber Probe Analytical Platform for Early Diagnosis of Dengue Fever," *Materials Science and Engineering: C* 109 (2020): 110629, 2020.110629, https://doi.org/10.1016/j.msec.

148. S. Hosseini, P. Azari, M. Aeinehvand, et al., "Intrant ELISA: A Novel Approach to Fabrication of Electrospun Fiber Mat-Assisted Biosensor Platforms and Their Integration Within Standard Analytical Well Plates," *Applied Sciences* 6 (2016): 336, https://doi.org/10.3390/app6110336.

149. V. O. Arruda, L. R. G. Filho, and A. F. Neves, "Aptamer-Associated Colorimetric Reverse Transcription Loop-Mediated Isothermal Amplification Assay for Detection of Dengue Virus," *Microbiology Spectrum* 12 (2024): e0358323, https://doi.org/10.1128/spectrum.03583-23.

150. F. Farokhinejad, R. E. Lane, R. J. Lobb, et al., "Generation of Nanoyeast Single-Chain Variable Fragments as High-Avidity Biomaterials for Dengue Virus Detection," *ACS Biomaterials Science & Engineering* 7 (2021): 5850–5860, https://doi.org/10.1021/acsbiomaterials.1c01001.

151. E. Farahmand, F. Ibrahim, S. Hosseini, et al., "A Novel Approach for Application of Nylon Membranes in the Biosensing Domain," *Applied Surface Science* 353 (2015): 1310–1319, https://doi.org/10.1016/j.apsusc.2015.07.004.

152. R. Ramírez-Navarro, P. Polesnak, J. Reyes-Leyva, et al., "A Magnetic Immunoconjugate Nanoplatform for Easy Colorimetric Detection of the NS1 Protein of Dengue Virus in Infected Serum," *Nanoscale Advances* 2 (2020): 3017–3026, https://doi.org/10.1039/d0na00251h.

153. L. Lin, X. Fan, Y. Yan, et al., "In Situ Amplified Colorimetric Immunoassay Coupled With a Dual-Enzyme-Functionalized UiO-66(Ce) Framework for Quantitative Detection of the Dengue Virus," *Sensors & Diagnostics* 4 (2025): 75–81, https://doi.org/10.1039/D4SD00335G.

154. M. Z. Khalil, R. Tariq, M. I. Majeed, et al., "SERS-Based Serological Profiling of Dengue and Typhoid Fever Advancing Infectious Disease Diagnostics Using PCA and PLS-DA," *Plasmonics* (2025), https://doi.org/10.1007/s11468-025-02854-3.

155. A. Shahzadi, S. Yaseen, M. I. Majeed, et al., "SERS Combined With Multivariate Data Analysis for Differentiation of Blood Serum Samples From Malaria and Dengue Patients After 50 kDa Membrane Filtration," *Plasmonics* (2025), https://doi.org/10.1007/s11468-025-02860-5.

156. N. F. Ismail, K. Y. Lee, N. S. Mohd Hadis, et al., "Nano Silver-Coated Porous Silicon-Based Surface-Enhanced Raman Spectroscopy Substrate for Low-Concentration Dengue NS1 Protein Detection," *Journal of Applied Spectroscopy* 91 (2024): 480–488, https://doi.org/10.1007/s10812-024-01744-6.

157. S. K. Gahlaut, D. Savargaonkar, C. Sharan, S. Yadav, P. Mishra, and J. P. Singh, "SERS Platform for Dengue Diagnosis From Clinical Samples Employing a Hand Held Raman Spectrometer," *Analytical Chemistry* 92 (2020): 2527–2534, https://doi.org/10.1021/acs.analchem.9b04129.

158. C. Song, J. Zhang, Y. Liu, et al., "Highly Sensitive SERS Assay of DENV Gene via a Cascade Signal Amplification Strategy of Localized Catalytic Hairpin Assembly and Hybridization Chain Reaction," *Sensors and Actuators B: Chemical* 325 (2020): 128970, https://doi.org/10.1016/j.snb.2020.128970.

159. A. M. Paul, Z. Fan, S. S. Sinha, et al., "Bio-Conjugated Gold Nanoparticle Based SERS Probe for Ultrasensitive Identification of Mosquito-Borne Viruses Using Raman Fingerprinting," *Journal of Physical Chemistry C* 119 (2015): 23669–23675, https://doi.org/10.1021/acs.jpcc.5b07387.

160. M. A. Mustapa, A. A. Latif, N. A. Awang, F. D. Muhammad, and A. S. Amir Hamzah, "Modulating Surface-Enhanced Raman Scattering With Hybrid-Gold Nanostructures: PCA-Driven Insights Into Ultrasensitive Detection of Dengue Virus NS1 IgG," *Microchemical Journal* 210 (2025): 112996, https://doi.org/10.1016/j.microc.2025.112996.

161. F. Farokhinejad, J. Li, L. E. Hugo, C. B. Howard, A. Wuethrich, and M. Trau, "Detection of Dengue Virus 2 With Single Infected Mosquito Resolution Using Yeast Affinity Bionanofragments and Plasmonic SERS Nanoboxes," *Analytical Chemistry* 94 (2022): 14177–14184, https://doi.org/10.1021/acs.analchem.2c02012.

162. T. Zhu, J. He, W. Chen, et al., "Development of Peptide-Based Chemiluminescence Enzyme Immunoassay (CLEIA) for Diagnosis of Dengue Virus Infection in Human," *Analytical Biochemistry* 556 (2018): 112–118, https://doi.org/10.1016/j.ab.2018.06.030.

163. R. Arts, I. den Hartog, S. E. Zijlema, V. Thijssen, S. H. E. van der Beelen, and M. Merkx, "Detection of Antibodies in Blood Plasma Using Bioluminescent Sensor Proteins and a Smartphone," *Analytical Chemistry* 88 (2016): 4525–4532, https://doi.org/10.1021/acs.analchem.6b00534.

164. A. García, L. Franco, M. Pirez-Gomez, et al., "Feasibility Study of an Optical Caustic Plasmonic Light Scattering Sensor for Human Serum Anti-Dengue Protein E Antibody Detection," *Diagnostics* 7 (2017): 47, https://doi.org/10.3390/diagnostics7030047.

165. M. Jeningsih, L. L. Tan, A. Ulianas, et al., "Sandwich-Type DNA Micro-Optode Based on Gold-Latex Spheres Label for Reflectance Dengue Virus Detection," *Sensors* 20 (2020): 1820, https://doi.org/10.3390/s20071820.

166. N. F. Mazlan, L. L. Tan, N. H. A. Karim, et al., "Acrylic-Based Genosensor Utilizing Metal Salphen Labeling Approach for Reflectometric Dengue Virus Detection," *Talanta* 198 (2019): 358–370, https://doi.org/10.1016/j.talanta.2019.02.036.

167. N. D. Jamaluddin, N. F. Mazlan, L. L. Tan, N. Y. M. Yusof, and B. Khalid, "G-Quadruplex Microspheres-Based Optical RNA Biosensor for Arthropod-Borne Virus Pathogen Detection: A Proof-of-Concept With Dengue Serotype 2," *International Journal of Biological Macromolecules* 199 (2022): 1–9, https://doi.org/10.1016/j.ijbiomac.2021.12.047.

168. E. Ariffin, L. Tan, N. Abd Karim, and L. Yook Heng, "Optical DNA Biosensor Based on Square-Planar Ethyl Piperidine Substituted Nickel (II) Salphen Complex for Dengue Virus Detection," *Sensors* 18 (2018): 1173, https://doi.org/10.3390/s18041173.

169. N.-F. Mazlan, L. L. Tan, N. H. A. Karim, L. Y. Heng, and M. I. H. Reza, "Optical Biosensing Using Newly Synthesized Metal Salphen Complexes: A Potential DNA Diagnostic Tool," *Sensors and Actuators B: Chemical* 242 (2017): 176–188, https://doi.org/10.1016/j.snb.2016.11.032.

170. N. M. Amin, Y. M. Kamil, N. H. Z. Abidin, F. H. Mustafa, and M. H. A. Bakar, "Chitosan-Integrated Single-Mode Tapered Optical Fiber DENV II E Protein Sensor," *IEEE Sensors Journal* 21 (2021): 20069–20077, https://doi.org/10.1109/JSEN.2021.3098297.

171. Y. M. Kamil, M. H. A. Bakar, M. H. Yaacob, A. Syahir, H. N. Lim, and M. A. Mahdi, "Dengue E Protein Detection Using a Graphene Oxide Integrated Tapered Optical Fiber Sensor," *IEEE Journal of Selected Topics in Quantum Electronics* 25 (2019): 1–8, https://doi.org/10.1109/JSTQE.2018.2846044.

172. Y. Mustapha Kamil, M. H. AbuBakar, S. Al-Rekabi, M. Yaacob, A. Syahir, and M. A. Mahdi, "PAMAM-Graphene Oxide-Integrated Microfiber Sensor for Label-Free Dengue II E Protein Detection," *IEEE Journal of Selected Topics in Quantum Electronics* 27 (2021): 1–6, https://doi.org/10.1109/JSTQE.2021.3064050.

173. Y. Mustapha Kamil, S. H. Al-Rekabi, M. H. Yaacob, et al., "Detection of Dengue Using PAMAM Dendrimer Integrated Tapered Optical Fiber Sensor," *Scientific Reports* 9 (2019): 13483, https://doi.org/10.1038/s41598-019-49891-7.

174. A. H. M. I. Ferdous, M. R. Miah, K. S. Noor, et al., "Design and Optimization of Photonic Crystal Fibre THz Bio-Sensor for Extremely Impressible Identification of Dengue," *IET Nanodielectrics* 7 (2024): 307–320, https://doi.org/10.1049/nde2.12091.

175. S. Alam, M. M. Khan, and R. K. Sonkar, "Dengue Disease Detection via a Minimal Area 2D Photonic Crystal Nanocavity-Based Refractive Index Optical Biosensor: Numerical Analysis," *Applied Optics* 64 (2025): 4615–4624, https://doi.org/10.1364/AO.562766.

176. D. M. Nasr, S. I. Mostafa, and M. A. El Naggar, "Enhanced 1D Photonic Crystal Biosensor for Blood Components and Blood Infection Detection," *European Physical Journal D* 78 (2024): 57, https://doi.org/10.1140/epjd/s10053-024-00838-2.

177. J. M. Pitarke, V. M. Silkin, E. V. Chulkov, and P. M. Echenique, "Theory of Surface Plasmons and Surface-Plasmon Polaritons," *Reports on Progress in Physics* 70 (2007): 1–87, https://doi.org/10.1088/0034-4885/70/1/R01.

178. S. S. Hinman, K. S. McKeating, and Q. Cheng, "Surface Plasmon Resonance: Material and Interface Design for Universal Accessibility," *Analytical Chemistry* 90 (2018): 19–39, https://doi.org/10.1021/acs.analchem.7b04251.

179. Y. Hang, A. Wang, and N. Wu, "Plasmonic Silver and Gold Nanoparticles: Shape- and Structure-Modulated Plasmonic Functionality for Point-of-Caring Sensing, Bio-Imaging and Medical Therapy," *Chemical Society Reviews* 53 (2024): 2932–2971, https://doi.org/10.1039/d3cs00793f.

180. H. Y. Nukaly and S. A. Ansari, "An Insight Into the Physicochemical Properties of Gold Nanoparticles in Relation to Their Clinical and Diagnostic Applications," *Cureus* 15 (2023): e37803, https://doi.org/10.7759/cureus.37803.

181. A. Loiseau, V. Asila, G. Boitel-Aullen, M. Lam, M. Salmain, and S. Boujday, "Silver-Based Plasmonic Nanoparticles for and Their Use in Biosensing," *Biosensors* 9 (2019): 78, https://doi.org/10.3390/bios9020078.

182. D. A. Muller, M. J. Landsberg, C. Bletchly, et al., "Structure of the Dengue Virus Glycoprotein Non-Structural Protein 1 by Electron Microscopy and Single-Particle Analysis," *Journal of General Virology* 93 (2012): 771–779, https://doi.org/10.1099/vir.0.039321-0.

183. D. Jessy Mercy, K. Girigoswami, and A. Girigoswami, "A Mini Review on Biosensor Advancements-Emphasis on Quantum Dots," *Results in Chemistry* 7 (2024): 101271, https://doi.org/10.1016/j.rechem.2023.101271.

184. E. Soršak, J. V. Valh, Š. K. Urek, and A. Lobnik, "Application of PAMAM Dendrimers in Optical Sensing," *Analyst* 140 (2015): 976–989, https://doi.org/10.1039/C4AN00825A.

185. Y. Zhu, S. Murali, W. Cai, et al., "Graphene and Graphene Oxide: Synthesis, Properties, and Applications," *Advanced Materials* 22 (2010): 3906–3924, https://doi.org/10.1002/adma.201001068.

186. D. T. Nurrohman and N. F. Chiu, "A Review of Graphene-Based Surface Plasmon Resonance and Surface-Enhanced Raman Scattering Biosensors: Current Status and Future Prospects," *Nanomaterials* 11 (2021): 216, https://doi.org/10.3390/nano11010216.

187. A. Gosai, K. Khondakar, X. Ma, and M. Ali, "Application of Functionalized Graphene Oxide Based Biosensors for Health Monitoring: Simple Graphene Derivatives to 3D Printed Platforms," *Biosensors* 11 (2021): 384, https://doi.org/10.3390/bios11100384.

188. M. A. Badshah, N. Y. Koh, A. W. Zia, N. Abbas, Z. Zahra, and M. W. Saleem, "Recent Developments in Plasmonic Nanostructures for Metal Enhanced Fluorescence-Based Biosensing," *Nanomaterials* 10 (2020): 1749, https://doi.org/10.3390/nano10091749.

189. Y. Jeong, Y. M. Kook, K. Lee, and W. G. Koh, "Metal Enhanced Fluorescence (MEF) for Biosensors: General Approaches and a Review of Recent Developments," *Biosensors and Bioelectronics* 111 (2018): 102–116, https://doi.org/10.1016/j.bios.2018.04.007.

190. A. Camarca, A. Varriale, A. Capo, et al., "Emergent Biosensing Technologies Based on Fluorescence Spectroscopy and Surface Plasmon Resonance," *Sensors* 21 (2021): 906, https://doi.org/10.3390/s21030906.

191. W. Nawrot, K. Drzozga, S. Baluta, J. Cabaj, and K. Malecha, "A Fluorescent Biosensors for Detection Vital Body Fluids' Agents," *Sensors* 18 (2018): 2357, https://doi.org/10.3390/s18082357.

192. Z. Ramezani and M. Thompson, "Quantum Dots in Viral and Bacterial Detection," in *Quantum Dots in Bioanalytical Chemistry and Medicine* (Royal Society of Chemistry, 2023), 142.

193. M. Chern, R. Toufanian, and A. M. Dennis, "Quantum Dot to Quantum Dot Förster Resonance Energy Transfer: Engineering Materials for Visual Color Change Sensing," *Analyst* 145 (2020): 5754–5767, https://doi.org/10.1039/d0an00746c.

194. K. R. Singh, P. Sridevi, and R. P. Singh, "Potential Applications of Peptide Nucleic Acid in Biomedical Domain," *Engineering Reports* 2 (2020): e12238, https://doi.org/10.1002/eng2.12238.

195. M. Díaz-González, A. de la Escosura-Muñiz, M. T. Fernandez-Argüelles, F. J. G. Alonso, and J. M. Costa-Fernandez, "Quantum Dot Bioconjugates for Diagnostic Applications," in *Surface-Modified Nanobiomaterials for Electrochemical and Biomedicine Applications* (Springer International Publishing, 2020), 133.

196. Q. Liu, X. Ding, Y. Pang, et al., "New Insights Into the Safety Assessment of Quantum Dots: Potential Release Pathways, Environmental Transformations, and Health Risks," *Environmental Science: Nano* 9 (2022): 3277–3311, https://doi.org/10.1039/D2EN00252C.

197. G. Genchi, M. S. Sinicropi, G. Lauria, A. Carocci, and A. Catalano, "The Effects of Cadmium Toxicity," *International Journal of Environmental Research and Public Health* 17 (2020): 3782, https://doi.org/10.3390/ijerph17113782.

198. S. K. Krishnan, E. Singh, P. Singh, M. Meyyappan, and H. S. Nalwa, "A Review on Graphene-Based Nanocomposites for Electrochemical and Fluorescent Biosensors," *RSC Advances* 9 (2019): 8778–8881, https://doi.org/10.1039/C8RA09577A.

199. E. Morales-Narváez and A. Merkoçi, "Graphene Oxide as an Optical Biosensing Platform: A Progress Report," *Advanced Materials* 31 (2019): e1805043, https://doi.org/10.1002/adma.201805043.

200. A. M. de Figueiredo, J. C. Glória, Y. O. Chaves, W. L. L. Neves, and L. A. M. Mariúba, "Diagnostic Applications of Microsphere-Based Flow Cytometry: A Review," *Experimental Biology and Medicine* 247 (2022): 1852–1861, https://doi.org/10.1177/15353702221113856.

201. H. Graham, D. J. Chandler, and S. A. Dunbar, "The Genesis and Evolution of Bead-Based Multiplexing," *Methods* 158 (2019): 2–11, https://doi.org/10.1016/j.ymeth.2019.01.007.

202. Z. Chen, G. Luo, J. Ren, et al., "Recent Advances in and Application of Fluorescent Microspheres for Multiple Nucleic Acid Detection," *Biosensors* 14 (2024): 265, https://doi.org/10.3390/bios14060265.

203. V. Calzada, "Aptamers in Diagnostic and Molecular Imaging Applications," *Advances in Biochemical Engineering/Biotechnology* 174 (2020): 141–160, https://doi.org/10.1007/10_2019_115.

204. P. Kumar Kulabhusan, B. Hussain, and M. Yüce, "Current Perspectives on Aptamers as Diagnostic Tools and Therapeutic Agents," *Pharmaceutics* 12 (2020): 646, https://doi.org/10.3390/pharmaceutics12070646.

205. H. Yu, Z. Chen, Y. Liu, O. Alkhamis, Z. Song, and Y. Xiao, "Fabrication of Aptamer-Modified Paper Electrochemical Devices for On-Site Biosensing," *Angewandte Chemie International Edition* 60 (2021): 2993–3000, https://doi.org/10.1002/anie.202008231.

206. S. E. Seo, E. Ryu, J. Kim, C. J. Shin, and O. S. Kwon, "Fluorophore-Encapsulated Nanobeads for On-Site, Rapid, and Sensitive Lateral Flow Assay," *Sensors and Actuators B: Chemical* 381 (2023): 133364, https://doi.org/10.1016/j.snb.2023.133364.

207. R. Chen, Y. Hu, M. Chen, et al., "Naked-Eye Detection of Hepatitis B Surface Antigen Using Gold Nanoparticles Aggregation and Catalase-Functionalized Polystyrene Nanospheres," *ACS Omega* 6 (2021): 9828–9833, https://doi.org/10.1021/acsomega.1c00507.

208. C. Contado, D. Mehn, D. Gilliland, and L. Calzolai, "Characterization Methods for Studying Protein Adsorption on Nano-Polystyrene Beads," *Journal of Chromatography A* 1606 (2019): 460383, https://doi.org/10.1016/j.chroma.2019.460383.

209. S. Moulay, "Functionalized Polystyrene and Polystyrene-Containing Material Platforms for Various Applications," *Polymer-Plastics*

Technology and Engineering 57 (2018): 1045–1092, https://doi.org/10.1080/03602559.2017.1370109.

210. X. Wang, X. Wang, X. Sui, et al., "ZnO Nanowire/NiO Foam 3D Nanostructures for High-Performance Ethylene Glycol Sensing," *Sensors and Actuators B: Chemical* 400 (2024): 134918, https://doi.org/10.1016/j.snb.2023.134918.

211. O. Parkash, C. Yean, and R. Shueb, "Screen Printed Carbon Electrode Based Electrochemical Immunosensor for the Detection of Dengue NS1 Antigen," *Diagnostics* 4 (2014): 165–180, https://doi.org/10.3390/diagnostics4040165.

212. Y. Wu, J. Feng, G. Hu, E. Zhang, and H. H. Yu, "Colorimetric Sensors for Chemical and Biological Sensing Applications," *Sensors* 23 (2023): 2749, https://doi.org/10.3390/s23052749.

213. V. X. T. Zhao, T. I. Wong, X. T. Zheng, Y. N. Tan, and X. Zhou, "Colorimetric Biosensors for Point-of-Care Virus Detections," *Materials Science for Energy Technologies* 3 (2020): 237–249, https://doi.org/10.1016/j.mset.2019.10.002.

214. S. A. F. Kusuma, J. A. Harmonis, R. Pratiwi, and A. N. Hasanah, "Gold Nanoparticle-Based Colorimetric Sensors: Properties and Application in Detection of Heavy Metals and Biological Molecules," *Sensors* 23 (2023): 8172, https://doi.org/10.3390/s23198172.

215. S. P. Dubey, M. Lahtinen, and M. Sillanpää, "Green Synthesis and Characterizations of Silver and Gold Nanoparticles Using Leaf Extract of *Rosa rugosa*," *Colloids and Surfaces, A: Physicochemical and Engineering Aspects* 364 (2010): 34–41, https://doi.org/10.1016/j.colsurfa.2010.04.023.

216. H. Aldewachi, T. Chalati, M. N. Woodroofe, N. Bricklebank, B. Sharrack, and P. Gardiner, "Gold Nanoparticle-Based Colorimetric Biosensors," *Nanoscale* 10 (2018): 18–33, https://doi.org/10.1039/C7NR06367A.

217. F. Najafzadeh, F. Ghasemi, and M. R. Hormozi-Nezhad, "Anti-Aggregation of Gold Nanoparticles for Metal Ion Discrimination: A Promising Strategy to Design Colorimetric Sensor Arrays," *Sensors and Actuators B: Chemical* 270 (2018): 545–551, https://doi.org/10.1016/j.snb.2018.05.065.

218. A. Davydova and M. Vorobyeva, "Aptamer-Based Biosensors for the Colorimetric Detection of Blood Biomarkers: Paving the Way to Clinical Laboratory Testing," *Biomedicines* 10 (2022): 1606, https://doi.org/10.3390/biomedicines10071606.

219. R. Stephanie, M. W. Kim, S. H. Kim, J.-K. Kim, C. Y. Park, and T. J. Park, "Recent Advances of Bimetallic Nanomaterials and Its Nanocomposites for Biosensing Applications," *Trends in Analytical Chemistry* 135 (2021): 116159, https://doi.org/10.1016/j.trac.2020.116159.

220. M. Wang, L. Jin, P. Hang-Mei Leung, et al., "Advancements in Magnetic Nanoparticle-Based Biosensors for Point-of-Care Testing," *Frontiers in Bioengineering and Biotechnology* 12 (2024): 1393789, https://doi.org/10.3389/fbioe.2024.1393789.

221. Y. Zhao, Y. Shang, Z. Wang, et al., "The Recent Advances of High-Throughput Biosensors for Rapid Detection of Foodborne Pathogens," *TrAC, Trends in Analytical Chemistry* 176 (2024): 117736, https://doi.org/10.1016/j.trac.2024.117736.

222. G. Qiu, Z. Gai, Y. Tao, J. Schmitt, G. A. Kullak-Ublick, and J. Wang, "Dual-Functional Plasmonic Photothermal Biosensors for Highly Accurate Severe Acute Respiratory Syndrome Coronavirus 2 Detection," *ACS Nano* 14 (2020): 5268–5277, https://doi.org/10.1021/acsnano.0c02439.

223. T. Yu, H. Xu, Y. Zhao, et al., "Aptamer Based High Throughput Colorimetric Biosensor for Detection of *Staphylococcus aureus*," *Scientific Reports* 10 (2020): 9190, https://doi.org/10.1038/s41598-020-66105-7.

224. T. Wasilewski, W. Kamysz, and J. Gębicki, "AI-Assisted Detection of Biomarkers by Sensors and Biosensors for Early Diagnosis and Monitoring," *Biosensors* 14 (2024): 356, https://doi.org/10.3390/bios14070356.

225. R. Singh, V. Yadav, A. K. Dhillon, A. Sharma, T. Ahuja, and S. Siddhanta, "Emergence of Raman Spectroscopy as a Probing Tool for Theranostics," *Nanotheranostics* 7 (2023): 216–235, https://doi.org/10.7150/ntno.81936.

226. K. Kneipp, Y. Wang, H. Kneipp, et al., "Single Molecule Detection Using Surface-Enhanced Raman Scattering (SERS)," *Physical Review Letters* 78 (1997): 1667–1670, https://doi.org/10.1103/PhysRevLett.78.1667.

227. K. A. Willets and R. P. Van Duyne, "Localized Surface Plasmon Resonance Spectroscopy and Sensing," *Annual Review of Physical Chemistry* 58 (2007): 267–297, https://doi.org/10.1146/annurev.physchem.58.032806.104607.

228. M. Sun, Y. Huang, L. Xia, X. Chen, and H. Xu, "The pH-Controlled Plasmon-Assisted Surface Photocatalysis Reaction of 4-Aminothiophenol to p,p′-Dimercaptoazobenzene on Au, Ag, and Cu Colloids," *Journal of Physical Chemistry C* 115 (2011): 9629–9636, https://doi.org/10.1021/jp201002v.

229. R. Pilot, R. Signorini, C. Durante, L. Orian, M. Bhamidipati, and L. Fabris, "A Review on Surface-Enhanced Raman Scattering," *Biosensors* 9 (2019): 57, https://doi.org/10.3390/bios9020057.

230. J. Wang, Z. Xu, and D. G. Kotsifaki, "Plasmonic and Metamaterial Biosensors: A Game-Changer for Virus Detection," *Sensors & Diagnostics* 2 (2023): 600–619, https://doi.org/10.1039/D2SD00217E.

231. M. T. Yaraki and Y. N. Tan, "Metal Nanoparticles-Enhanced Biosensors: Synthesis, Design and Applications in Fluorescence Enhancement and Surface-Enhanced Raman Scattering," *Chemistry – An Asian Journal* 15 (2020): 3180–3208, https://doi.org/10.1002/asia.202000847.

232. Y. Zhang, C. Xue, Y. Xu, et al., "Metal-Organic Frameworks Based Surface-Enhanced Raman Spectroscopy Technique for Ultra-Sensitive Biomedical Trace Detection," *Nano Research* 16 (2023): 2968–2979, https://doi.org/10.1007/s12274-022-4914-1.

233. M. Shafi, P. Duan, W. Liu, et al., "Recyclable Surface-Enhanced Raman Spectroscopy (SERS) Platform Fabricated With Ag-Decorated Znse Nanowires and Metamaterial," *Sensors and Actuators B: Chemical* 380 (2023): 133410, https://doi.org/10.1016/j.snb.2023.133410.

234. M. J. Oliveira, A. Dalot, E. Fortunato, et al., "Microfluidic SERS Devices: Brightening the Future of Bioanalysis," *Discover Materials* 2 (2022): 12, https://doi.org/10.1007/s43939-022-00033-3.

235. A. H.-W. Yeh, C. Norn, Y. Kipnis, et al., "De Novo Design of Luciferases Using Deep Learning," *Nature* 614 (2023): 774–780, https://doi.org/10.1038/s41586-023-05696-3.

236. D. Cialla-May, A. Bonifacio, A. Markin, et al., "Recent Advances of Surface Enhanced Raman Spectroscopy (SERS) in Optical Biosensing," *TrAC, Trends in Analytical Chemistry* 181 (2024): 117990, https://doi.org/10.1016/j.trac.2024.117990.

237. F. Zeng, W. Duan, B. Zhu, et al., "Paper-Based Versatile Surface-Enhanced Raman Spectroscopy Chip With Smartphone-Based Raman Analyzer for Point-of-Care Application," *Analytical Chemistry* 91 (2019): 1064–1070, https://doi.org/10.1021/acs.analchem.8b04441.

238. A. C. Love and J. A. Prescher, "Seeing (and Using) the Light: Recent Developments in Bioluminescence Technology," *Cell Chemical Biology* 27 (2020): 904–920, https://doi.org/10.1016/j.chembiol.2020.07.022.

239. A. Roda, M. Mirasoli, E. Michelini, et al., "Progress in Chemical Luminescence-Based Biosensors: A Critical Review," *Biosensors and Bioelectronics* 76 (2016): 164–179, https://doi.org/10.1016/j.bios.2015.06.017.

240. K. Akimoto, Y. Shinmen, M. Sumida, et al., "Luminol Chemiluminescence Reaction Catalyzed by a Microbial Peroxidase,"

Analytical Biochemistry 189 (1990): 182–185, https://doi.org/10.1016/0003-2697(90)90104-h.

241. W. R. G. Baeyens, S. G. Schulman, A. C. Calokerinos, et al., "Chemiluminescence-Based Detection: Principles and Analytical Applications in Flowing Streams and in Immunoassays," *Journal of Pharmaceutical and Biomedical Analysis* 17 (1998): 941–953, https://doi.org/10.1016/s0731-7085(98)00062-4.

242. E. M. Gross, S. S. Maddipati, and S. M. Snyder, "A Review of Electrogenerated Chemiluminescent Biosensors for Assays in Biological Matrices," *Bioanalysis* 8 (2016): 2071–2089, https://doi.org/10.4155/bio-2016-0178.

243. J. Hiblot, Q. Yu, M. D. B. Sabbadini, et al., "Luciferases With Tunable Emission Wavelengths," *Angewandte Chemie International Edition* 56 (2017): 14556–14560, https://doi.org/10.1002/anie.201708277.

244. A. J. Syed and J. C. Anderson, "Applications of Bioluminescence in Biotechnology and Beyond," *Chemical Society Reviews* 50 (2021): 5668–5705, https://doi.org/10.1039/d0cs01492c.

245. J. G. Morin and J. W. Hastings, "Energy Transfer in a Bioluminescent System," *Journal of Cellular Physiology* 77 (1971): 313–318, https://doi.org/10.1002/jcp.1040770305.

246. E. Hwang, J. Song, and J. Zhang, "Integration of Nanomaterials and Bioluminescence Resonance Energy Transfer Techniques for Sensing Biomolecules," *Biosensors* 9 (2019): 42, https://doi.org/10.3390/bios9010042.

247. K. Tenda, B. van Gerven, R. Arts, Y. Hiruta, M. Merkx, and D. Citterio, "Paper-Based Antibody Detection Devices Using Bioluminescent BRET-Switching Sensor Proteins," *Angewandte Chemie International Edition* 57 (2018): 15369–15373, https://doi.org/10.1002/anie.201808070.

248. M. P. Hall, J. Unch, B. F. Binkowski, et al., "Engineered Luciferase Reporter From a Deep Sea Shrimp Utilizing a Novel Imidazopyrazinone Substrate," *ACS Chemical Biology* 7 (2012): 1848–1857, https://doi.org/10.1021/cb3002478.

249. L. Biewenga, B. J. H. M. Rosier, and M. Merkx, "Engineering With Nanoluc: A Playground for the Development of Bioluminescent Protein Switches and Sensors," *Biochemical Society Transactions* 48 (2020): 2643–2655, https://doi.org/10.1042/BST20200440.

250. R. Arts, S. J. Aper, and M. Merkx, "Engineering BRET-Sensor Proteins," *Methods in Enzymology* 589 (2017): 87–114, https://doi.org/10.1016/bs.mie.2017.01.010.

251. M. Calabretta, D. Gregucci, H. Martínez-Pérez-Cejuela, and E. Michelini, "A Luciferase Mutant With Improved Brightness and Stability for Whole-Cell Bioluminescent Biosensors and In Vitro Biosensing," *Biosensors* 12 (2022): 742, https://doi.org/10.3390/bios12090742.

252. W. He, M. Wang, P. Cheng, Y. Liu, and M. You, "Recent Advances of Upconversion Nanoparticles-Based Lateral Flow Assays for Point-of-Care Testing," *TrAC, Trends in Analytical Chemistry* 176 (2024): 117735, https://doi.org/10.1016/j.trac.2024.117735.

253. J. Bacart, C. Corbel, R. Jockers, S. Bach, and C. Couturier, "The BRET Technology and Its Application to Screening Assays," *Biotechnology Journal* 3 (2008): 311–324, https://doi.org/10.1002/biot.200700222.

254. A. Giannetti and S. Tombelli, "Aptamer Optical Switches: From Biosensing to Intracellular Sensing," *Sensors and Actuators Reports* 3 (2021): 100030, https://doi.org/10.1016/j.snr.2021.100030.

255. B. Roda, S. K. Deo, G. O'Connor, et al., "Shining Light on Biosensors: Chemiluminescence and Bioluminescence in Enabling Technologies," *TrAC, Trends in Analytical Chemistry* 180 (2024): 117975, https://doi.org/10.1016/j.trac.2024.117975.

256. T. Liyanage, M. Lai, and G. Slaughter, "Label-Free Tapered Optical Fiber Plasmonic Biosensor," *Analytica Chimica Acta* 1169 (2021): 338629, https://doi.org/10.1016/j.aca.2021.338629.

257. B. A. Taha, N. Ali, N. M. Sapiee, et al., "Comprehensive Review Tapered Optical Fiber Configurations for Sensing Application: Trend and Challenges," *Biosensors* 11 (2021): 253, https://doi.org/10.3390/bios11080253.

258. W. Zhang, X. Lang, X. Liu, et al., "Advances in Tapered Optical Fiber Sensor Structures: From Conventional to Novel and Emerging," *Biosensors* 13 (2023): 644, https://doi.org/10.3390/bios13060644.

259. P. Wang, G. Brambilla, M. Ding, Y. Semenova, Q. Wu, and G. Farrell, "High-Sensitivity, Evanescent Field Refractometric Sensor Based on a Tapered, Multimode Fiber Interference," *Optics Letters* 36 (2011): 2233–2235, https://doi.org/10.1364/OL.36.002233.

260. G. Proll, G. Markovic, P. Fechner, F. Proell, and G. Gauglitz, "Reflectometric Interference Spectroscopy," *Methods in Molecular Biology* 1571 (2017): 207–220, https://doi.org/10.1007/978-1-4939-6848-0_13.

261. R. W. Peeling, H. Artsob, J. L. Pelegrino, et al., "Evaluation of Diagnostic Tests: Dengue," *Nature Reviews Microbiology* 8 (2010): S30–S37, https://doi.org/10.1038/nrmicro2459.

262. H. Lee, J. H. Ryu, H. S. Park, et al., "Comparison of Six Commercial Diagnostic Tests for the Detection of Dengue Virus Non-Structural-1 Antigen and IgM/IgG Antibodies," *Annals of Laboratory Medicine* 39 (2019): 566–571, https://doi.org/10.3343/alm.2019.39.6.566.

263. O. Parkash and R. Shueb, "Diagnosis of Dengue Infection Using Conventional and Biosensor Based Techniques," *Viruses* 7 (2015): 5410–5427, https://doi.org/10.3390/v7102877.

264. N. Raafat, S. D. Blacksell, and R. J. Maude, "A Review of Dengue Diagnostics and Implications for Surveillance and Control," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 113 (2019): 653–660, https://doi.org/10.1093/trstmh/trz068.

265. M. Haider, S. Yousaf, A. Zaib, A. Sarfraz, Z. Sarfraz, and I. Cherrez-Ojeda, "Diagnostic Accuracy of Various Immunochromatographic Tests for NS1 Antigen and IgM Antibodies Detection in Acute Dengue Virus Infection," *International Journal of Environmental Research and Public Health* 19 (2022): 8756, https://doi.org/10.3390/ijerph19148756.

266. T. N. A. Mat Jusoh and R. H. Shueb, "Performance Evaluation of Commercial Dengue Diagnostic Tests for Early Detection of Dengue in Clinical Samples," *Journal of Tropical Medicine* 2017 (2017): 4687182, https://doi.org/10.1155/2017/4687182.

267. D. W. Vaughn, S. Green, S. Kalayanarooj, et al., "Dengue in the Early Febrile Phase: Viremia and Antibody Responses," *Journal of Infectious Diseases* 176 (1997): 322–330, https://doi.org/10.1086/514048.

268. D. J. Gubler, "Dengue and Dengue Hemorrhagic Fever," *Clinical Microbiology Reviews* 11 (1998): 480–496, https://doi.org/10.1128/CMR.11.3.480.

269. J. L. Muñoz-Jordán, C. S. Collins, E. Vergne, et al., "Highly Sensitive Detection of Dengue Virus Nucleic Acid in Samples From Clinically Ill Patients," *Journal of Clinical Microbiology* 47 (2009): 927–931, https://doi.org/10.1128/JCM.01564-08.

270. B. T. Teoh, S. S. Sam, K. K. Tan, et al., "Early Detection of Dengue Virus by Use of Reverse Transcription-Recombinase Polymerase Amplification," *Journal of Clinical Microbiology* 53 (2015): 830–837, https://doi.org/10.1128/JCM.02648-14.

271. J. L. Frazer and R. Norton, "Dengue: A Review of Laboratory Diagnostics in the Vaccine Age," *Journal of Medical Microbiology* 73 (2024): 001833, https://doi.org/10.1099/jmm.0.001833.

272. B. H. Kok, H. T. Lim, C. P. Lim, N. S. Lai, C. Y. Leow, and C. H. Leow, "Dengue Virus Infection—A Review of Pathogenesis, Vaccines, Diagnosis and Therapy," *Virus Research* 324 (2023): 199018, https://doi.org/10.1016/j.virusres.2022.199018.

273. S. Alcon, A. Talarmin, M. Debruyne, A. Falconar, V. Deubel, and M. Flamand, "Enzyme-Linked Immunosorbent Assay Specific to Dengue Virus Type 1 Nonstructural Protein NS1 Reveals Circulation of the Antigen

in the Blood During the Acute Phase of Disease in Patients Experiencing Primary or Secondary Infections," *Journal of Clinical Microbiology* 40 (2002): 376–381, https://doi.org/10.1128/JCM.40.02.376-381.2002.

274. J. K. Lim, N. Alexander, and G. L. Di Tanna, "A Systematic Review of the Economic Impact of Rapid Diagnostic Tests for Dengue," *BMC Health Services Research* 17 (2017): 850, https://doi.org/10.1186/s12913-017-2789-8.

275. S. Mitra, R. Choudhari, H. Nori, et al., "Comparative Evaluation of Validity and Cost-Benefit Analysis of Rapid Diagnostic Test (RDT) Kits in Diagnosis of Dengue Infection Using Composite Reference Criteria: A Cross-Sectional Study From South India," *Journal of Vector Borne Diseases* 53 (2016): 30–36, https://doi.org/10.4103/0972-9062.179216.

276. Y. Lubell, T. Althaus, S. D. Blacksell, et al., "Modelling the Impact and Cost-Effectiveness of Biomarker Tests as Compared With Pathogen-Specific Diagnostics in the Management of Undifferentiated Fever in Remote Tropical Settings," *PLoS One* 11 (2016): e0152420, https://doi.org/10.1371/journal.pone.0152420.

277. T. Bhardwaj, L. N. Ramana, and T. K. Sharma, "Current Advancements and Future Road Map to Develop Assured Microfluidic Biosensors for Infectious and Non-Infectious Diseases," *Biosensors* 12 (2022): 357, https://doi.org/10.3390/bios12050357.

278. T. Joseph, D. Kar Mahapatra, A. Esmaeili, et al., "Nanoparticles: Taking a Unique Position in Medicine," *Nanomaterials* 13 (2023): 574, https://doi.org/10.3390/nano13030574.

279. R. Foulkes, E. Man, J. Thind, S. Yeung, A. Joy, and C. Hoskins, "The Regulation of Nanomaterials and Nanomedicines for Clinical Application: Current and Future Perspectives," *Biomaterials Science* 8 (2020): 4653–4664, https://doi.org/10.1039/d0bm00558d.

280. V. Sainz, J. Conniot, A. I. Matos, et al., "Regulatory Aspects on Nanomedicines," *Biochemical and Biophysical Research Communications* 468 (2015): 504–510, https://doi.org/10.1016/j.bbrc.2015.08.023.

281. F. J. Tovar-Lopez, "Recent Progress in Micro- and Nanotechnology-Enabled Sensors for Biomedical and Environmental Challenges," *Sensors* 23 (2023): 5406, https://doi.org/10.3390/s23125406.

282. S. K. Vashist, A. G. Venkatesh, K. Mitsakakis, et al., "Nanotechnology-Based Biosensors and Diagnostics: Technology Push Versus Industrial/Healthcare Requirements," *BioNanoScience* 2 (2012): 115–126, https://doi.org/10.1007/s12668-012-0047-4.

283. R. Prasad, A. Ghosh, V. Patel, et al., "Voices of Nanomedicine: Blueprint Guidelines for Collaboration in Addressing Global Unmet Medical Needs," *ACS Nano* 19 (2025): 2979–2991, https://doi.org/10.1021/acsnano.4c13513.

284. P. J. Gawne, M. Ferreira, M. Papaluca, J. Grimm, and P. Decuzzi, "New Opportunities and Old Challenges in the Clinical Translation of Nanotheranostics," *Nature Reviews Materials* 8 (2023): 783–798, https://doi.org/10.1038/s41578-023-00581-x.

285. N. Desai, D. Rana, M. Patel, N. Bajwa, R. Prasad, and L. K. Vora, "Nanoparticle Therapeutics in Clinical Perspective: Classification, Marketed Products, and Regulatory Landscape," *Small* 21 (2025): e2502315, https://doi.org/10.1002/smll.202502315.

286. D. Bhatia, S. Paul, T. Acharjee, and S. S. Ramachairy, "Biosensors and Their Widespread Impact on Human Health," *Sensors International* 5 (2024): 100257, https://doi.org/10.1016/j.sintl.2023.100257.

287. M. Ramalingam, A. Jaisankar, L. Cheng, et al., "Impact of Nanotechnology on Conventional and Artificial Intelligence-Based Biosensing Strategies for the Detection of Viruses," *Discover Nano* 18 (2023): 58, https://doi.org/10.1186/s11671-023-03842-4.

288. M. Hemdan, M. A. Ali, A. S. Doghish, et al., "Innovations in Biosensor Technologies for Healthcare Diagnostics and Therapeutic Drug Monitoring: Applications, Recent Progress, and Future Research Challenges," *Sensors* 24 (2024): 5143, https://doi.org/10.3390/s24165143.

289. A. Mokhtarzadeh, R. Eivazzadeh-Keihan, P. Pashazadeh, et al., "Nanomaterial-Based Biosensors for Detection of Pathogenic Virus," *Trends in Analytical Chemistry* 97 (2017): 445–457, https://doi.org/10.1016/j.trac.2017.10.005.

290. A. Cernian, B. Tiganoaia, I. Sacala, A. Pavel, and A. Iftemi, "Patientdatachain: A Blockchain-Based Approach to Integrate Personal Health Records," *Sensors* 20 (2020): 6538, https://doi.org/10.3390/s20226538.

291. S. Arumugam, D. A. M. Colburn, and S. K. Sia, "Biosensors for Personal Mobile Health: A System Architecture Perspective," *Advanced Materials Technologies* 5 (2020): 1900720, https://doi.org/10.1002/admt.201900720.

292. C. Meliana, J. Liu, P. L. Show, and S. S. Low, "Biosensor in Smart Food Traceability System for Food Safety and Security," *Bioengineered* 15 (2024): 2310908, https://doi.org/10.1080/21655979.2024.2310908.

293. C. Lino, S. Barrias, R. Chaves, F. Adega, P. Martins-Lopes, and J. R. Fernandes, "Biosensors as Diagnostic Tools in Clinical Applications," *Biochimica et Biophysica Acta (BBA)—Reviews on Cancer* 1877 (2022): 188726, https://doi.org/10.1016/j.bbcan.2022.188726.

294. S. Campuzano and J. M. Pingarrón, "Electrochemical Affinity Biosensors: Pervasive Devices With Exciting Alliances and Horizons Ahead," *ACS Sensors* 8 (2023): 3276–3293, https://doi.org/10.1021/acssensors.3c01172.

295. E. Eksin and A. Erdem, "Recent Progress on Optical Biosensors Developed for Nucleic Acid Detection Related to Infectious Viral Diseases," *Micromachines* 14 (2023): 295, https://doi.org/10.3390/mi14020295.

296. H. K. Choi and J. Yoon, "Nanotechnology-Assisted Biosensors for the Detection of Viral Nucleic Acids: An Overview," *Biosensors* 13 (2023): 208, https://doi.org/10.3390/bios13020208.

297. Y. S. Sun, "Use of Microarrays as a High-Throughput Platform for Label-Free Biosensing," *SLAS Technology* 20 (2015): 334–353, https://doi.org/10.1177/2211068215577570.

298. K. Chen, Z. Shen, G. Wang, et al., "Research Progress of CRISPR-Based Biosensors and Bioassays for Molecular Diagnosis," *Frontiers in Bioengineering and Biotechnology* 10 (2022): 986233, https://doi.org/10.3389/fbioe.2022.986233.

299. A. Kumaran, N. Jude Serpes, T. Gupta, et al., "Advancements in CRISPR-Based Biosensing for Next-Gen Point of Care Diagnostic Application," *Biosensors* 13 (2023): 202, https://doi.org/10.3390/bios13020202.

300. M. Kumari, V. Gupta, N. Kumar, and R. K. Arun, "Microfluidics-Based Nanobiosensors for Healthcare Monitoring," *Molecular Biotechnology* 66 (2024): 378–401, https://doi.org/10.1007/s12033-023-00760-9.

301. G. Gharib, I. Bütün, Z. Muganlı, et al., "Biomedical Applications of Microfluidic Devices: A Review," *Biosensors* 12 (2022): 1023, https://doi.org/10.3390/bios12111023.

302. S. Gimondi, H. Ferreira, R. L. Reis, and N. M. Neves, "Microfluidic Devices: A Tool for Nanoparticle Synthesis and Performance Evaluation," *ACS Nano* 17 (2023): 14205–14228, https://doi.org/10.1021/acsnano.3c01117.

303. M. A. Prescott, M. T. Koesdjojo, D. T. Mandrell, and M. K. Pastey, "Development of a Rapid Point-of-Care Dengue Virus Type 2 Infection Diagnostic Assay Using Recombinase Polymerase Amplification and Lateral Flow Device," *Frontiers in Cellular and Infection Microbiology* 15 (2025): 1578549, https://doi.org/10.3389/fcimb.2025.1578549.

304. W. Zhang, L. Cui, Y. Wang, et al., "An Integrated ddPCR Lab-on-a-Disc Device for Rapid Screening of Infectious Diseases," *Biosensors* 14 (2024): 2, https://doi.org/10.3390/bios14010002.

305. P. Pormrungruang, S. Phanthanawiboon, S. Jessadaluk, et al., "Metal Oxide Nanostructures Enhanced Microfluidic Platform for Efficient and Sensitive Immunofluorescence Detection of Dengue

Virus," *Nanomaterials* 13 (2023): 2846, https://doi.org/10.3390/nano13212846.

306. S. Lee, L. Bi, H. Chen, et al., "Recent Advances in Point-of-Care Testing of COVID-19," *Chemical Society Reviews* 52 (2023): 8500–8530, https://doi.org/10.1039/d3cs00709j.

307. M. H. Prabowo, T. Chalermwatanachai, W. Surareungchai, and P. Rijiravanich, "Portable Paper-Based Immunoassay Combined With Smartphone Application for Colorimetric and Quantitative Detection of Dengue NS1 Antigen," *Journal of Visualized Experiments* 203 (2024): e66130, https://doi.org/10.3791/66130.

308. N. Moser, L. S. Yu, J. Rodriguez Manzano, et al., "Quantitative Detection of Dengue Serotypes Using a Smartphone-Connected Handheld Lab-on-Chip Platform," *Frontiers in Bioengineering and Biotechnology* 10 (2022): 892853, https://doi.org/10.3389/fbioe.2022.892853.

309. A. Priye, S. W. Bird, Y. K. Light, C. S. Ball, O. A. Negrete, and R. J. Meagher, "A Smartphone-Based Diagnostic Platform for Rapid Detection of Zika, Chikungunya, and Dengue Viruses," *Scientific Reports* 7 (2017): 44778, https://doi.org/10.1038/srep44778.

310. M. R. Hasan, P. Sharma, S. Singh, and J. Narang, "Smartphone-Integrated Wireless Portable Potentiostat to Develop 5th-Generation Dengue Pocket Aptasensor Toward Portronicx-Approach," *ACS Applied Bio Materials* 7 (2024): 2299–2308, https://doi.org/10.1021/acsabm.3c01299.

311. N. Zulkifli, N. Che-Kamaruddin, A. Hazan, T. Kim-Kee, S. Rajagopal, and S. AbuBakar, "Utility and Usability of a Dengue NS1 Rapid Diagnostic as a Self-Test," *Tropical Medicine and Health* 53 (2025): 28, https://doi.org/10.1186/s41182-025-00705-9.

312. B. A. Miu and A. Dinischiotu, "New Green Approaches in Nanoparticles Synthesis: An Overview," *Molecules* 27 (2022): 6472, https://doi.org/10.3390/molecules27196472.

313. A. Puri, P. Mohite, S. Maitra, et al., "From Nature to Nanotechnology: The Interplay of Traditional Medicine, Green Chemistry, and Biogenic Metallic Phytonanoparticles in Modern Healthcare Innovation and Sustainability," *Biomedicine & Pharmacotherapy* 170 (2024): 116083, https://doi.org/10.1016/j.biopha.2023.116083.

314. B. P. Backx, "Green Nanotechnology: Only the Final Product That Matters?," *Natural Product Research 36* 36 (2022): 3507–3509, https://doi.org/10.1080/14786419.2020.1855168.

315. S. S. Shankar, A. Rai, A. Ahmad, and M. Sastry, "Rapid Synthesis of Au, Ag, and Bimetallic Au Core-Ag Shell Nanoparticles Using Neem (*Azadirachta indica*) Leaf Broth," *Journal of Colloid and Interface Science* 275 (2004): 496–502, https://doi.org/10.1016/j.jcis.2004.03.003.

316. M. N. Nadagouda, N. Iyanna, J. Lalley, C. Han, D. D. Dionysiou, and R. S. Varma, "Synthesis of Silver and Gold Nanoparticles Using Antioxidants From Blackberry, Blueberry, Pomegranate, and Turmeric Extracts," *ACS Sustainable Chemistry & Engineering* 2 (2014): 1717–1723, https://doi.org/10.1021/sc500237k.

317. A. S. Reddy, C. Y. Chen, C. C. Chen, et al., "Biological Synthesis of Gold and Silver Nanoparticles Mediated by the Bacteria *Bacillus subtilis*," *Journal of Nanoscience and Nanotechnology* 10 (2010): 6567–6574, https://doi.org/10.1166/jnn.2010.2519.

318. P. Pourali, V. Dzmitruk, O. Benada, M. Svoboda, and V. Benson, "Conjugation of Microbial-Derived Gold Nanoparticles to Different Types of Nucleic Acids: Evaluation of Transfection Efficiency," *Scientific Reports* 13 (2023): 14669, https://doi.org/10.1038/s41598-023-41567-7.

319. H. Majdi, R. Salehi, M. Pourhassan-Moghaddam, S. Mahmoodi, Z. Poursalehi, and S. Vasilescu, "Antibody Conjugated Green Synthesized Chitosan-Gold Nanoparticles for Optical Biosensing," *Colloid and Interface Science Communications* 33 (2019): 100207, https://doi.org/10.1016/j.colcom.2019.100207.

320. V. Buk, E. Emregul, and K. C. Emregul, "Alginate Copper Oxide Nano-Biocomposite as a Novel Material for Amperometric Glucose Biosensing," *Materials Science and Engineering: C* 74 (2017): 307–314, https://doi.org/10.1016/j.msec.2016.12.003.

321. N. M. Noah and P. M. Ndangili, "Green Synthesis of Nanomaterials From Sustainable Materials for Biosensors and Drug Delivery," *Sensors International* 3 (2022): 100166, https://doi.org/10.1016/j.sintl.2022.100166.

322. S. Jafarzadeh, N. Oladzadabbasabadi, M. A. Dheyab, et al., "Emerging Trends in Smart and Sustainable Nano-Biosensing: The Role of Green Nanomaterials," *Industrial Crops and Products* 223 (2025): 120108, https://doi.org/10.1016/j.indcrop.2024.120108.

323. S. Augustine, A. Venkadesh, S. Kaushal, E. Lee, M. Ajaj, and N. E. Lee, "Point-of-Care Testing: The Convergence of Innovation and Accessibility in Diagnostics," *Analytical Chemistry* 97 (2025): 9569–9599, https://doi.org/10.1021/acs.analchem.4c07075.

324. N. T. Darwish, S. D. Sekaran, and S. M. Khor, "Point-of-Care Tests: A Review of Advances in the Emerging Diagnostic Tools for Dengue Virus Infection," *Sensors and Actuators B: Chemical* 255 (2018): 3316–3331, https://doi.org/10.1016/j.snb.2017.09.159.

325. C. Merzbacher and D. A. Oyarzún, "Applications of Artificial Intelligence and Machine Learning in Dynamic Pathway Engineering," *Biochemical Society Transactions* 51 (2023): 1871–1879, https://doi.org/10.1042/BST20221542.

326. C. Wang, T. He, H. Zhou, Z. Zhang, and C. Lee, "Artificial Intelligence Enhanced Sensors—Enabling Technologies to Next-Generation Healthcare and Biomedical Platform," *Bioelectronic Medicine* 9 (2023): 17, https://doi.org/10.1186/s42234-023-00118-1.

327. C. D. Flynn and D. Chang, "Artificial Intelligence in Point-of-Care Biosensing: Challenges and Opportunities," *Diagnostics* 14 (2024): 1100, https://doi.org/10.3390/diagnostics14111100.

328. Z. Khoshbin, M. R. Housaindokht, M. Izadyar, M. R. Bozorgmehr, and A. Verdian, "Recent Advances in Computational Methods for Biosensor Design," *Biotechnology and Bioengineering* 118 (2021): 555–578, https://doi.org/10.1002/bit.27618.

329. M. Atabay, F. Inci, and Y. Saylan, "Computational Studies for the Development of Extracellular Vesicle-Based Biosensors," *Biosensors and Bioelectronics* 277 (2025): 117275, https://doi.org/10.1016/j.bios.2025.117275.

330. K. H. Yu, A. L. Beam, and I. S. Kohane, "Artificial Intelligence in Healthcare," *Nature Biomedical Engineering* 2 (2018): 719–731, https://doi.org/10.1038/s41551-018-0305-z.

331. M. Alavinejad, M. Shirzad, M. J. Javid-Naderi, A. Rahdar, S. Fathi-Karkan, and S. Pandey, "Smart Nanomedicines Powered by Artificial Intelligence: A Breakthrough in Lung Cancer Diagnosis and Treatment," *Medical Oncology* 42 (2025): 134, https://doi.org/10.1007/s12032-025-02680-x.

332. S. S. Arya, S. B. Dias, H. F. Jelinek, L. J. Hadjileontiadis, and A. M. Pappa, "The Convergence of Traditional and Digital Biomarkers Through AI-Assisted Biosensing: A New Era in Translational Diagnostics?," *Biosensors and Bioelectronics* 235 (2023): 115387, https://doi.org/10.1016/j.bios.2023.115387.

333. J. M. Scavuzzo, F. Trucco, M. Espinosa, et al., "Modeling Dengue Vector Population Using Remotely Sensed Data and Machine Learning," *Acta Tropica* 185 (2018): 167–175, https://doi.org/10.1016/j.actatropica.2018.05.003.

334. A. L. Buczak, P. T. Koshute, S. M. Babin, B. H. Feighner, and S. H. Lewis, "A Data-Driven Epidemiological Prediction Method for Dengue Outbreaks Using Local and Remote Sensing Data," *BMC Medical Informatics and Decision Making* 12 (2012): 124, https://doi.org/10.1186/1472-6947-12-124.

335. S. Q. Ong, P. Isawasan, A. M. M. Ngesom, H. Shahar, A. M. Lasim, and G. Nair, "Predicting Dengue Transmission Rates by Comparing Different Machine Learning Models With Vector Indices and

Meteorological Data," *Scientific Reports* 13 (2023): 19129, https://doi.org/10.1038/s41598-023-46342-2.

336. A. Sebastianelli, D. Spiller, R. Carmo, et al., "A Reproducible Ensemble Machine Learning Approach to Forecast Dengue Outbreaks," *Scientific Reports* 14 (2024): 3807, https://doi.org/10.1038/s41598-024-52796-9.

337. V. Machault, A. Yébakima, M. Etienne, et al., "Mapping Entomological Dengue Risk Levels in Martinique Using High-Resolution Remote-Sensing Environmental Data," *ISPRS International Journal of Geo-Information* 3 (2014): 1352–1371, https://doi.org/10.3390/ijgi3041352.

338. M. Barik, A. Pattanayak, S. Mukherjee, S. Koner, S. Tewari, and S. Vaishnav, "AI Technology for Detecting Dengue: A Systematic Review," *International Journal of Mosquito Research* 11 (2024): 141–143, https://doi.org/10.22271/23487941.2024.v11.i6a.815.

339. H. Mayrose, G. M. Bairy, N. Sampathila, S. Belurkar, and K. Saravu, "Machine Learning-Based Detection of Dengue From Blood Smear Images Utilizing Platelet and Lymphocyte Characteristics," *Diagnostics* 13 (2023): 220, https://doi.org/10.3390/diagnostics13020220.

340. V. J. Lee, A. Chow, X. Zheng, et al., "Simple Clinical and Laboratory Predictors of Chikungunya Versus Dengue Infections in Adults," *PLoS Neglected Tropical Diseases* 6 (2012): e1786, https://doi.org/10.1371/journal.pntd.0001786.

341. X. Bi, X. Ai, Z. Wu, L. L. Lin, Z. Chen, and J. Ye, "Artificial Intelligence-Powered Surface-Enhanced Raman Spectroscopy for Biomedical Applications," *Analytical Chemistry* 97 (2025): 6826–6846, https://doi.org/10.1021/acs.analchem.4c06584.

342. F. M. Yrad, J. M. Castañares, and E. C. Alocilja, "Visual Detection of Dengue-1 RNA Using Gold Nanoparticle-Based Lateral Flow Biosensor," *Diagnostics* 9 (2019): 74, https://doi.org/10.3390/diagnostics9030074.

343. J. Calvillo-Arbizu, I. Román-Martínez, and J. Reina-Tosina, "Internet of Things in Health: Requirements, Issues, and Gaps," *Computer Methods and Programs in Biomedicine* 208 (2021): 106231, https://doi.org/10.1016/j.cmpb.2021.106231.

344. M. A. Sadique, S. Yadav, R. Khan, and A. K. Srivastava, "Engineered Two-Dimensional Nanomaterials Based Diagnostics Integrated With Internet of Medical Things (IoMT) for COVID-19," *Chemical Society Reviews* 53 (2024): 3774–3828, https://doi.org/10.1039/d3cs00719g.

345. B. Pradhan, S. Bhattacharyya, and K. Pal, "IoT-Based Applications in Healthcare Devices," *Journal of Healthcare Engineering* 2021 (2021): 6632599, https://doi.org/10.1155/2021/6632599.

346. H. Zhu, P. Podesva, X. Liu, et al., "IoT PCR for Pandemic Disease Detection and Its Spread Monitoring," *Sensors and Actuators B: Chemical* 303 (2020): 127098, https://doi.org/10.1016/j.snb.2019.127098.

347. S. Karolcik, V. Manginas, H. Q. Chanh, et al., "Towards a Machine-Learning Assisted Non-Invasive Classification of Dengue Severity Using Wearable PPG Data: A Prospective Clinical Study," *EBioMedicine* 104 (2024): 105164, https://doi.org/10.1016/j.ebiom.2024.105164.

348. M. Ibrar, S. Y. Huang, Z. McCurtain, et al., "Modular Anti-Counterfeit Tags Formed by Template-Assisted Self-Assembly of Plasmonic Nanocrystals and Authenticated by Machine Learning," *Advanced Functional Materials* 34 (2024): 2400842, https://doi.org/10.1002/adfm.202400842.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplementary Table S1: Key advantages and limitations of conventional diagnostic methods for DENV infection