Oxford Immunotec

Oxford Immunotec Limited
143 Park Drive
Milton Park, Abingdon
Oxfordshire, OX14 4SE, UK

Tel: +44 (0) 1235 442 780
Fax: +44 (0) 1235 442 781
www.oxfordimmunotec.com
Company No. 04516079

To whom it may concern,

We are pleased to be able to announce an update to the T-SPOT.*COVID* test package insert - PI-T-SPOT.COVID-IVD-UK v3 – which has been updated to PI-T-SPOT.COVID-IVD-UK v4. The update reflects additional published data supporting the use of the T-SPOT.*COVID* test for vaccine monitoring. There are no changes to either the kit contents nor the process of running the kit. Therefore, you can confidently use all T-SPOT.*COVID* test kits with the new PI (v4), even if they were purchased with the previous PI (v3).

Kits will begin shipping with the new PI from early March. After this date you may receive a kit containing either PI v3 or PI v4 (for a period of up to 6 months). The kit should be treated the same irrespective of which version of the PI you receive. The updated PI (v4) is included with this communication, and is available from the Oxford Immunotec website www.tspotcovid.com

What changes have been made to the PI?

The intended use statement has been modified to allow for more applications as more data becomes available. The use of the test to detect an immune response after vaccination is now included in the intended use statement alongside the use of the test to detect an immune response to infection. The introduction has also been updated to show the data supporting the use of the test for vaccine monitoring in immunocompetent and immunosuppressed individuals from multiple vaccine studies.

Why have we updated the PI?

The T-SPOT.*COVID* test was launched on March 4th 2021. The first person in the world to receive a dose of any COVID vaccine as part of a mass-vaccination program received their vaccine on 8th December 2020. As such the T-SPOT.*COVID* test was launched before it was possible to evaluate its use in vaccination. There is now published data available for use of the test beyond infection. This enables us to extend the intended use to include monitoring the immune response to vaccination, in line with how the needs of clinicians and the medical community have changed as the pandemic has progressed.

Data supporting the use of T-SPOT.*COVID* for vaccine monitoring.

The T-SPOT.*COVID* test and its sister product the T-SPOT *Discovery* SARS-CoV-2 assay (for research use only) have both been used extensively to better understand the T cell response to vaccination. The T-SPOT.*COVID* test was developed from the T-SPOT *Discovery* SARS-CoV-2 assay and shares some peptides with the assay. The tests have been used extensively as part of our partnership with the UK vaccine taskforce to measure the T cell response of vaccine candidates being developed for mass vaccination programs. In fact the test has now been used for more than 30,000 samples in studies carried out by our Oxford Diagnostics Laboratory service in the UK alone, as well as being cited in over 40 publications to date. The vaccine studies include the UK Human challenge trial, COV-AD, Direct, Reach and COM-COV amongst others and the tests are being increasingly used in a routine setting.
In the multi-cohort clinical study COM-COV, homologous vs. heterologous vaccine strategies were investigated in a non-inferiority test to accelerate vaccine deployment. The study authors showed that all four groups tested - ChAd/ChAd, BNT/BNT, ChAd/BNT, and BNT/ChAd (ChAd = Astra Zeneca, BNT =

BioNTec COVID vaccines) developed effective antibody and T cell responses after the 2nd dose of vaccine, showing that heterologous vaccination can induce a robust immune response comparable or better than homologous vaccination[1].
Further, the second COM-COV study revealed that a booster dose with NVX after ChAd was superior to homologous vaccination with ChAd, inducing a higher humoral and cellular response. Neutralizing antibody levels against Beta and Delta were depleted across all groups, independent of the vaccination schedule; however, T cell responses remained stable[2].
The T-SPOT.*COVID* test was used to show in a clinical study by Simon et al that in B cell depleted patients both vaccination and infection could generate a T cell response, but antibodies were only present with infection. SARS-CoV-2 vaccination failed to trigger significant humoral immune responses in patients treated with B cell depletion (rituximab therapy). The test showed that both SARS-CoV-2 vaccination and SARS-CoV-2 infection triggered a T cell mediated immune response, even in the absence of peripheral B cells and the authors suggested that this T cell mediated immunity was potentially protective in the absence of B cells after vaccination in this patient group[3].
The study by Lindemann et al investigated both antibody and T cell responses in haemopoietic stem cell recipients in comparison to healthy controls pre- and post-vaccination. In haemopoietic stem cell transplant recipients T cell responses were present, but were reduced compared to healthy controls, indicating the importance of T cell testing in this cohort to better understand the breadth of the immune response to vaccination[4].
Individuals with a low B cell count due to infliximab showed impaired serological responses but cellular responses were unaffected. Following the 1st vaccine dose, fewer immunosuppressed subjects had antibody and T cell responses compared to the control. However, following the 2nd vaccine dose, more subjects in both the immunosuppressed and control groups showed T cell responses, with no significant difference in percentages between the two groups[5].
Lower humoral (antibody) responses were seen in a further study with patients treated with B-cell depleting therapeutics; however, no difference was observed in T cell responses between the vaccinated immunosuppressed and the vaccinated immunocompetent[6].

Importance of T cells – Broad response and long lasting virus control

It is well-documented that T cells are involved in controlling and clearing viral infections of the respiratory system. While COVID-19 vaccines have been shown to induce robust antibody responses in the majority of vaccinated individuals, there are now data supporting some key areas where T cells are likely to be of particular importance in COVID-19[7,8].

Response to new variants:

Despite the high number of mutations that allow the Omicron variant to evade the humoral response, the T cell response remains largely intact between the ancestral SARS-CoV-2 spike protein and Omicron[9].
Recent findings indicate that Omicron infection in vaccinated individuals may not only protect against Omicron but cross-protect against other variants as well; however, unvaccinated individuals may not develop a cross-protection[10].
In spite of a number of unknowns, the lack of humoral immunity to variants seems to correlate with prolonged infection, and robust T cell responses seem to limit disease severity in patients that didn't develop a humoral response[11,12]. As more variants of concern continue to develop, T cells may become even more important as a vaccine induced mechanism for protection.

Long lasting compared to neutralising antibodies:

It has been shown, in a sample of 503 healthcare workers, that after priming following first vaccination, SARS-CoV-2 neutralizing antibody (NAb) levels drop dramatically, while the T cell response to spike protein remained stable. In this cohort NAb levels recovered after the second vaccination dose, with an accompanying distinct enrichment of CD4 T cells expressing IL-2[1]. T cells may offer long lasting protection following vaccination after antibody titres wane, with several studies showing that SARS-CoV-2 specific T cell immunity is maintained at least 6-9 months following primary infection[13].

The only CE marked test to separately measure both S and N protein induced T cell responses

Both S + N proteins are measured separately by the T-SPOT.*COVID* test. This could give additional information about the potential cause of the immune response. The immune response could be due to infection, vaccination or both infection and vaccination. The table below shows what each response could mean (using vaccinations approved by the European Medicines Agency as of February 2022).

Possible scenario	S response only	S & N response	N response only
Vaccination only	+		
Infection only	+	+	+
Vaccination plus infection	+	+	

Table 1. Any T cell response in the T-SPOT.*COVID* test could be due to vaccination or infection. By using both S + N proteins in separate test wells, test results may help to identify the likely source of the T cell response in some individuals.

Why the T-SPOT.*COVID* test is the right choice for my testing?

The ELISPOT platform utilized by the T-SPOT.*COVID* test isolates, counts and standardizes the T cells giving a sensitive, powerful, and reliable test. The T-SPOT.*COVID* test has already been used in a large and growing number of studies, and has been used to test thousands of samples for their T cell response to infection and vaccination. Having manufactured in excess of 20 million clinical T cell tests for TB infection and gained regulatory approval with the T-SPOT.*TB* test in over 50 countries (including the United States, Europe, Japan and China), we bring our wealth of experience to support you in your fight against COVID-19 by extending the use of T-SPOT.*COVID*, to make this an even more important tool.

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