

How do the two commercially available purified protein derivatives Aplisol and Tubersol compare when reading and interpreting the Tuberculin Skin Test?

The tuberculin skin test (TST) has served as the primary diagnostic tool used to screen patients at risk of tuberculosis (TB). Effective control of TB requires the quick detection of exposed contacts, an accurately placed and read TST, and then subsequent treatment if latent TB infection (LTBI) is diagnosed. An intradermal injection of purified protein derivative (PPD) from a broth culture of *Mycobacterium tuberculosis* is used to assess a patient's reactivity to common antigens of *M. tuberculosis*; this is the TST – the size of the resulting induration indicates whether infection with *M. tuberculosis* has occurred. Inherent in the TST is an inordinate amount of variability – injection of the PPD, reading of the TST, cross-reactivity with other *Mycobacterium* species, host immune factors, and inconsistency in the production of the PPD itself. Recognition and reduction of these variables is the key to an accurate diagnosis of LTBI in at-risk patients.

Two companies manufacture tuberculin in the United States; Parkdale Pharmaceuticals (Aplisol) and Pastuer Merieux Connaught (Tubersol); the comparative reference standard is the PPD-S2. There have been several studies to determine if Aplisol and Tubersol give comparable results when used to screen at-risk patients and TB diseased patients:

- A study in 2005 comparing an interferon-gamma release assay (IGRA) with Aplisol and Tubersol found 93% agreement between the PPD reagents on Day 2; discordant results were attributed to chance or lot variation. Eight persons had discordant readings on Day 2 between Aplisol and Tubersol. Results of IGRA agreed with Aplisol 4 times and Tubersol 4 times. The study population consisted of people considered at increased risk for LTBI (BCG-vaccinated and non-BCG-vaccinated - health care workers, laboratory personnel, patient care technicians, foreign-born, other hospital personnel with patient contact).¹
- In 2000, a study was conducted to determine if a new standard PPD-S2 was comparable to the old PPD-S1; and to assess the two commercial reagents (Aplisol and Tubersol) against the “gold standard” PPD-S1. Two distinct patient populations were tested – culture-positive TB-diseased subjects and uninfected, low-risk, non-BCG vaccinated subjects (both groups excluded HIV+ patients). There were no statistically significant differences between either reagent and PPD-S1 or PPD-S2. The sensitivity of the test in patients with TB was not significantly different (98.5% for Aplisol and 92% for Tubersol). The specificity at a 15mm cut point in the low risk group was not statistically different between the two standards [PPD-S1 (99.7%) and PPD-S2 (99.8%)] or between the standards and the commercial reagents [Aplisol (99.2%) and Tubersol (99.8%)]. The minimal variability noted between Aplisol and Tubersol (0.5 to 0.7%) was attributed to the variability inherent in the skin test procedure itself due to inter-observer variability and host variability.²

- In a 1999 JAMA report, Aplisol and Tubersol were compared side by side. In the low-risk population studied, Tubersol produced slightly smaller reactions ($2.5 \pm 3.6\text{mm}$) than Aplisol ($3.4 \pm 4.2\text{mm}$) but these differences did not result in any significant differences in the TST interpretations. In persons with culture positive tuberculosis Tubersol produced slightly smaller reactions, Aplisol slightly larger reactions than the standard PPD-S1 (Tubersol $14.9 \pm 6.0\text{ mm}$, Aplisol $16.3 \pm 5.6\text{mm}$ and PPD-S1 $16.2 \pm 6.4\text{mm}$).³
- TB culture-confirmed patients were TST-tested with Aplisol and Tubersol in a 1997 study. There were no significant differences between the two.⁴
- Previous reports of false positive TST reactions with Aplisol (TST repeated with Tubersol and determined negative) came from older studies prior to the new reference standard PPD-S2. They were flawed by small numbers of subjects, high-risk study populations, retesting done only for false positives, and omission of denominator data and TST lots.⁵⁻¹⁰

General Conclusions:

- **Study results do not show a significant difference in TST results with Aplisol or Tubersol.** Discrepancies noted were attributed to several factors:
 - Between observer variability (variability inherent in tuberculin testing)
 - Variability between lots
 - Aplisol has been postulated to contain more antigens shared with mycobacteria other than *M tuberculosis*; that might give some false positives when the general population is tested. However, this was not noted in the 2000 study²
 - Prior BCG vaccination may cloud results (most studies eliminated these patients from comparison)
- **When well controlled studies have compared either Aplisol or Tubersol to the standard PPD-S1 or PPD-S2 and to each other, there has been no significant difference in sensitivity or specificity or in the interpretation of tuberculin skin tests.**
- **Reports of “false positives” have usually occurred when screening large numbers of low risk persons is done with Aplisol.**
 - When this phenomenon occurs, it is important to evaluate whether these may represent true positives. Careful attention to technique of reading the test is important. It has been suggested that Aplisol may have a higher tendency to cause erythema and soft tissue swelling that is not true induration.^{6,8}

- If there is no evidence to suggest that the tests may represent true positives, further evaluation with an IGRA (QuantiFERON-Gold) should be considered. Repeat testing with Tubersol may also be considered.
- ***Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005* from the CDC acknowledges previous studies that show only a slight difference in reactivity (<1.0%) between Aplisol and Tubersol, but it does add the caveat:¹²**
 - “The difference in specificity, 98% versus 99% is limited. However, when applied in large institutional settings that test thousands of workers annually who are at low risk for infection with *M. tuberculosis*, this difference in specificity might affect the rate of positive TST results observed.”
 - The *Guideline* recommends that TB screening programs use one antigen (product) consistently recognizing that changes in products might make serial changes in TST results difficult to interpret.
- The Advisory Council for the Elimination of TB (ACET) did not agree with the conclusion that Aplisol and Tubersol equally perform as TST products. It has recommended the following when switching from Tubersol to Aplisol:¹¹
 - Notification to appropriate users when switching between products
 - A systematic assessment to exclude the possibility of ongoing transmission if a cluster of false-positive reactions in a health care setting is seen after a switch is made
 - Use Tubersol to retest if ongoing transmission is not a possibility or rule out a positive reaction by testing using the QuantiFERON-Gold (IGRA) test

References:

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